

4-19-00

jc804 U.S. PTO
04/18/00

Attorney Docket No.: 5697.200-US

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

FILING UNDER 37 C.F.R. 1.53(b)

Box Patent Application
Assistant Commissioner for Patents
Washington, DC 20231

Express Mail Label No. EL285639928US
Date of Deposit April 18, 2000

jc675 U.S. PTO
09/551740
04/18/00

Sir:

This is a request for filing an application under 37 C.F.R. 1.53(b) of
Applicant(s): Murray et al.

Title: New Compounds, Their Preparation and Use

71 pages of specification 0 sheets of drawings
3 sheets of Declaration and Power of Attorney

[x] The filing fee is calculated as follows:

Basic Fee:	\$690.00
Total Claims: $47 - 20 = 27 \times 18 =$	\$486.00
Independent Claims: $1 - 3 = 0 \times 78 =$	\$0
Total Fee:	\$1176.00

Priority of Danish application no. PA 1999 00533 filed on April 20, 1999 is claimed under 35 U.S.C. 119. A certified copy is submitted herewith.

Priority of U.S. provisional application no. 60/132,193 filed on May 3, 1999 is claimed under 35 U.S.C. 119.

Address all future communications to Steve T. Zelson, Esq., Novo Nordisk of North America, Inc., 405 Lexington Avenue, Suite 6400, New York, NY 10174-6401.

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Figure 1 consists of 12 sub-graphs, labeled (a) through (l), each showing a time course of a different physiological or behavioral parameter over a 10-minute period. The y-axis for all graphs ranges from 0 to 100. The x-axis for all graphs ranges from 0 to 10 minutes. The graphs show a general decrease in values during the intervention period, with some parameters showing a sharp drop at the start of the intervention.

- (a) Heart rate (b/min): Shows a sharp drop from approximately 100 to 80 at the start of the intervention, then remains relatively stable.
- (b) Blood pressure (mmHg): Shows a sharp drop from approximately 120 to 100 at the start of the intervention, then remains relatively stable.
- (c) Blood flow (ml/min): Shows a sharp drop from approximately 100 to 80 at the start of the intervention, then remains relatively stable.
- (d) Blood flow (ml/min): Shows a sharp drop from approximately 100 to 80 at the start of the intervention, then remains relatively stable.
- (e) Blood flow (ml/min): Shows a sharp drop from approximately 100 to 80 at the start of the intervention, then remains relatively stable.
- (f) Blood flow (ml/min): Shows a sharp drop from approximately 100 to 80 at the start of the intervention, then remains relatively stable.
- (g) Blood flow (ml/min): Shows a sharp drop from approximately 100 to 80 at the start of the intervention, then remains relatively stable.
- (h) Blood flow (ml/min): Shows a sharp drop from approximately 100 to 80 at the start of the intervention, then remains relatively stable.
- (i) Blood flow (ml/min): Shows a sharp drop from approximately 100 to 80 at the start of the intervention, then remains relatively stable.
- (j) Blood flow (ml/min): Shows a sharp drop from approximately 100 to 80 at the start of the intervention, then remains relatively stable.
- (k) Blood flow (ml/min): Shows a sharp drop from approximately 100 to 80 at the start of the intervention, then remains relatively stable.
- (l) Blood flow (ml/min): Shows a sharp drop from approximately 100 to 80 at the start of the intervention, then remains relatively stable.

Date: April 18, 2000

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Attorney Docket No.: 5697.200-US

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

EXPRESS MAIL CERTIFICATE

Box Patent Application
Assistant Commissioner for Patents
Washington, DC 20231

Re: U.S. Patent Application for
Title: New Compounds, Their Preparation and Use
Applicants: Murray et al.

Sir:

Express Mail Label No. EL285639928US

Date of Deposit : April 18, 2000

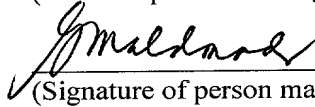
I hereby certify that the following attached paper(s) or fee

1. Filing Under 37 C.F.R. 1.53(b) (in duplicate)
2. Patent Application
3. Unexecuted Combined Declaration and Power of Attorney
4. Certified Copy of Priority Application

are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" under 37 C.F.R. 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, DC 20231.

Gina Maldonado

(Name of person mailing paper(s) or fee)



(Signature of person mailing paper(s) or fee)

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New Compounds, Their Preparation and Use

CROSS-REFERENCES TO RELATED APPLICATIONS

- 5 The present invention claims priority under 35 U.S.C. 119 of U.S. provisional application no. 60/132,193 filed May 3, 1999 and Danish application no. PA 1999 00533 filed April 20, 1999, the contents of which are fully incorporated herein by reference.

BACKGROUND OF THE INVENTION

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Field of the Invention

- 15 The present invention relates to novel compounds, pharmaceutical compositions containing them, methods for preparing the compounds and their use as medicaments. More specifically, compounds of the invention can be utilized in the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR).

Description of the Related Art

20

Coronary artery disease (CAD) is the major cause of death in Type 2 diabetic and metabolic syndrome patients (i.e. patients that fall within the 'deadly quartet' category of impaired glucose tolerance, insulin resistance, hypertriglyceridemia and/or obesity).

- 25 The hypolipidemic fibrates and antidiabetic thiazolidinediones separately display moderately effective triglyceride-lowering activities although they are neither potent nor efficacious enough to be a single therapy of choice for the dyslipidemia often observed in Type 2 diabetic or metabolic syndrome patients. The thiazolidinediones also potently lower circulating glucose levels of Type 2 diabetic animal models and humans. However, the fibrate class of compounds are without beneficial effects on glycemia. Studies on the molecular actions of
30 these compounds indicate that thiazolidinediones and fibrates exert their action by activating distinct transcription factors of the peroxisome proliferator-activated receptor (PPAR) family, resulting in increased and decreased expression of specific enzymes and apolipoproteins respectively, both key players in regulation of plasma triglyceride content. Fibrates, on the

one hand, are PPAR α activators, acting primarily in the liver. Thiazolidinediones, on the other hand, are high affinity ligands for PPAR γ acting primarily on adipose tissue.

Adipose tissue plays a central role in lipid homeostasis and the maintenance of energy balance in vertebrates. Adipocytes store energy in the form of triglycerides during periods of nutritional affluence and release it in the form of free fatty acids at times of nutritional deprivation. The development of white adipose tissue is the result of a continuous differentiation process throughout life. Much evidence points to the central role of PPAR γ activation in initiating and regulating this cell differentiation. Several highly specialized proteins are induced during adipocyte differentiation, most of them being involved in lipid storage and metabolism. The exact link from activation of PPAR γ to changes in glucose metabolism, most notably a decrease in insulin resistance in muscle, has not yet been clarified. A possible link is via free fatty acids such that activation of PPAR γ induces Lipoprotein Lipase (LPL), Fatty Acid Transport Protein (FATP) and Acyl-CoA Synthetase (ACS) in adipose tissue but not in muscle tissue. This, in turn, reduces the concentration of free fatty acids in plasma dramatically, and due to substrate competition at the cellular level, skeletal muscle and other tissues with high metabolic rates eventually switch from fatty acid oxidation to glucose oxidation with decreased insulin resistance as a consequence.

PPAR α is involved in stimulating β -oxidation of fatty acids. In rodents, a PPAR α -mediated change in the expression of genes involved in fatty acid metabolism lies at the basis of the phenomenon of peroxisome proliferation, a pleiotropic cellular response, mainly limited to liver and kidney and which can lead to hepatocarcinogenesis in rodents. The phenomenon of peroxisome proliferation is not seen in man. In addition to its role in peroxisome proliferation in rodents, PPAR α is also involved in the control of HDL cholesterol levels in rodents and humans. This effect is, at least partially, based on a PPAR α -mediated transcriptional regulation of the major HDL apolipoproteins, apo A-I and apo A-II. The hypotriglyceridemic action of fibrates and fatty acids also involves PPAR α and can be summarized as follows: (I) an increased lipolysis and clearance of remnant particles, due to changes in lipoprotein lipase and apo C-III levels, (II) a stimulation of cellular fatty acid uptake and their subsequent conversion to acyl-CoA derivatives by the induction of fatty acid binding protein and acyl-CoA synthase, (III) an induction of fatty acid oxidation pathways, (IV) a reduction in fatty acid and triglyceride synthesis, and finally (V) a decrease in VLDL

production. Hence, both enhanced catabolism of triglyceride-rich particles as well as reduced secretion of VLDL particles constitutes mechanisms that contribute to the hypolipidemic effect of fibrates.

- 5 A number of compounds have been reported to be useful in the treatment of hyperglycemia, hyperlipidemia and hypercholesterolemia (U.S. Pat. 5,306,726, PCT Publications nos. W091/19702, WO 95/03038, WO 96/04260, WO 94/13650, WO 94/01420, WO 97/36579, WO 97/25042, WO 95/17394, WO 99/08501, WO 99/19313 and WO 99/16758).

10 **SUMMARY OF THE INVENTION**

- 15 Glucose lowering as a single approach does not overcome the macrovascular complications associated with Type 2 diabetes and metabolic syndrome. Novel treatments of Type 2 diabetes and metabolic syndrome must therefore aim at lowering both the overt hypertriglyceridemia associated with these syndromes as well as alleviation of hyperglycemia.

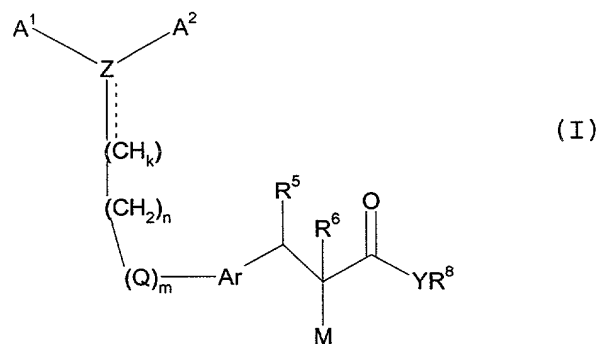
- 20 The clinical activity of fibrates and thiazolidinediones indicates that research for compounds displaying combined PPAR α and PPAR γ activation should lead to the discovery of efficacious glucose and triglyceride lowering drugs that have great potential in the treatment of Type 2 diabetes and the metabolic syndrome (i.e. impaired glucose tolerance, insulin resistance, hypertriglyceridemia and/or obesity).

DETAILED DESCRIPTION OF THE INVENTION

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Accordingly, the present invention relates to compounds of formula (I):

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- wherein A¹ and A² are independently of each other a 5-6 membered cyclic ring or a 9-10 membered bicyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro, cyano, formyl, or C₁₋₁₂-alkyl, (C₃₋₆-cycloalkyl)C₁₋₆-alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, C₁₋₁₂-alkoxy, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, acyl, acyloxy, hydroxyC₁₋₁₂-alkyl, amino, acylamino, C₁₋₁₂-alkyl-amino, C₁₋₆-dialkylamino, arylamino, arylalkylamino, aminoC₁₋₁₂-alkyl, C₁₋₁₂-alkoxycarbonyl, alkylaminocarbonyl, aryloxycarbonyl, arylalkoxycarbonyl, C₁₋₁₂-alkoxyC₁₋₁₂-alkyl, aryloxyC₁₋₁₂-alkyl, arylalkoxyC₁₋₁₂-alkyl, arylthio, C₁₋₁₂-alkylthio, thioC₁₋₁₂-alkyl, C₁₋₁₂-alkoxycarbonylamino, aryloxycarbonylamino, arylalkoxycarbonylamino, -COR¹, or -SO₂R², wherein R¹ and R² independently of each other are selected from hydroxy, halogen, perhalomethyl, C₁₋₆-alkoxy or amino optionally substituted with one or more C₁₋₆-alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

- Z is C or CR³, wherein R³ is hydrogen, halogen, perhalomethyl, C₁₋₁₂-alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, C₁₋₁₂-alkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, acyl, acyloxy, hydroxyC₁₋₁₂-alkyl, C₁₋₁₂-alkoxyC₁₋₁₂-alkyl, aryloxyC₁₋₁₂-alkyl, arylalkoxyC₁₋₁₂-alkyl, thioC₁₋₁₂-alkyl, -COR⁴, or -SO₂R¹¹, wherein R⁴ and R¹¹ independently of each other are selected from hydroxy, halogen, perhalomethyl, C₁₋₆-alkoxy or amino optionally substituted with one or more C₁₋₆-alkyl, perhalomethyl or aryl optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

Q is O, S or NR¹², wherein R¹² is hydrogen, perhalomethyl, C₁₋₁₂-alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, aryl, arylalkyl, heterocyclyl, heteroaryl, heteroarylalkyl, acyl, hydroxyC₁₋₁₂-alkyl, aminoC₁₋₁₂-alkyl, C₁₋₁₂-alkoxycarbonyl, aryloxyC₁₋₁₂-alkyl, thioC₁₋₁₂-alkyl, -COR¹³, or -SO₂R¹⁴, wherein R¹³ and R¹⁴ independently of each other are selected from hydroxy, perhalomethyl, C₁₋₆-alkoxy or amino optionally substituted with one or more C₁₋₆-alkyl, perhalomethyl or aryl optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

10

----- represents a single bond or a double bond;

15

Ar represents arylene, heteroarylene, or a divalent heterocyclic group each of which can optionally be substituted with one or more halogen, C₁₋₆-alkyl, amino, hydroxy, C₁₋₆-alkoxy or aryl;

20

R⁵ represents hydrogen, hydroxy, halogen, C₁₋₁₂-alkoxy, C₁₋₁₂-alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl or arylalkyl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano or R⁵ forms a bond together with R⁶;

25

R⁶ represents hydrogen, hydroxy, halogen, C₁₋₁₂-alkoxy, C₁₋₁₂-alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, acyl or arylalkyl optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano or R⁶ forms a bond together with R⁵;

M represents OR⁷, where R⁷ represents hydrogen, C₁₋₁₂-alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, aryl, arylalkyl, C₁₋₁₂-alkoxyC₁₋₁₂-alkyl, C₁₋₁₂-alkoxycarbonyl, aryloxyC₁₋₁₂-alkyl, C₁₋₁₂-alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl or heteroarylalkyl groups optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano or M represents COYR⁸;

30

R⁸ represents hydrogen, C₁₋₁₂-alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, aryl, arylalkyl, heterocyclyl, heteroaryl or heteroarylalkyl groups optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

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or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

In a preferred embodiment, the present invention is concerned with compounds of formula I wherein A¹ and A² are independently of each other a 5-6 membered cyclic ring or a 9-10 membered bicyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, C₁₋₆-alkyl, (C₃₋₆-cycloalkyl)C₁₋₆-alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₁₋₆-alkoxy, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, acyl, hydroxyC₁₋₆-alkyl, C₁₋₆-alkyl-amino, C₁₋₆-dialkylamino, arylamino, arylalkylamino, aminoC₁₋₆-alkyl, C₁₋₆-alkoxycarbonyl, alkylaminocarbonyl, aryloxycarbonyl, arylalkoxycarbonyl, C₁₋₆-alkoxyC₁₋₆-alkyl, aryloxyC₁₋₆-alkyl, or arylalkoxyC₁₋₆-alkyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein A¹ and A² are independently of each other a 5-6 membered cyclic ring or a 9-10 membered bicyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, C₁₋₆-alkyl, (C₃₋₆-cycloalkyl)C₁₋₆-alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₁₋₆-alkoxy, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, acyl, hydroxyC₁₋₆-alkyl, C₁₋₆-alkyl-amino, C₁₋₆-dialkylamino, arylamino, arylalkylamino, aminoC₁₋₆-alkyl, C₁₋₆-alkoxyC₁₋₆-alkyl, aryloxyC₁₋₆-alkyl, or arylalkoxyC₁₋₆-alkyl.

30 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein A¹ and A² are independently of each other a 5-6 membered cyclic ring or a 9-10 membered bicyclic ring, optionally substituted with one or more halogen, C₁₋₆-alkyl, C₁₋₆-alkoxy, or aryl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein A¹ and A² are independently of each other a 5-6 membered cyclic ring optionally substituted with one or more halogen, C₁₋₆-alkyl, C₁₋₆-alkoxy, or aryl.

5

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Z is a carbon atom at the end of a double bond, or Z is CR³, wherein R³ is hydrogen, halogen, perhalomethyl, C₁₋₁₂-alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, C₁₋₁₂-alkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, acyl, acyloxy, hydroxyC₁₋₁₂-alkyl, C₁₋₁₂-alkoxyC₁₋₁₂-alkyl, aryloxyC₁₋₁₂-alkyl, arylalkoxyC₁₋₁₂-alkyl, thioC₁₋₁₂-alkyl, -COR⁴, or -SO₂R¹¹, wherein R⁴ and R¹¹ independently of each other are selected from hydroxy, halogen, perhalomethyl, C₁₋₆-alkoxy or amino optionally substituted with one or more C₁₋₆-alkyl, perhalomethyl or aryl optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano.

15

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Z is a carbon atom at the end of a double bond, or Z is CR³, wherein R³ is hydrogen, halogen, perhalomethyl, C₁₋₆-alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₁₋₆-alkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, acyl, acyloxy, hydroxyC₁₋₆-alkyl, C₁₋₆-alkoxyC₁₋₆-alkyl, aryloxyC₁₋₆-alkyl, arylalkoxyC₁₋₆-alkyl, thioC₁₋₆-alkyl, -COR⁴, or -SO₂R¹¹, wherein R⁴ and R¹¹ independently of each other are selected from hydroxy, halogen, perhalomethyl, C₁₋₆-alkoxy or amino optionally substituted with one or more C₁₋₆-alkyl, perhalomethyl or aryl optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano.

25

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Z is a carbon atom at the end of a double bond, or Z is CR³, wherein R³ is hydrogen, halogen, perhalomethyl, C₁₋₆-alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₁₋₆-alkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, C₁₋₆-alkoxyC₁₋₆-alkyl, aryloxyC₁₋₆-alkyl, or arylalkoxyC₁₋₆-alkyl.

30

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Z is a carbon atom at the end of a double bond, or Z is CR³, wherein R³ is hydrogen.

- 5 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Q is O, S, or NR¹², wherein R¹² is hydrogen, perhalomethyl, C₁₋₆-alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, aryl, arylalkyl, heterocyclyl, heteroaryl, heteroarylalkyl, acyl, hydroxyC₁₋₆-alkyl, aminoC₁₋₆-alkyl, C₁₋₆-alkoxycarbonyl, aryloxy carbonyl, arylalkoxycarbonyl, C₁₋₆-alkoxyC₁₋₆-alkyl, aryloxyC₁₋₆-alkyl, arylalkoxyC₁₋₆-alkyl, thioC₁₋₆-alkyl, -COR¹³, or -SO₂R¹⁴, wherein R¹³ and R¹⁴ independently of each other are selected from hydroxy, perhalomethyl, C₁₋₆-alkoxy or amino optionally substituted with one or more C₁₋₆-alkyl, perhalomethyl or aryl optionally substituted with one or more halogen, or perhalomethyl.
- 10

- 15 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Q is O, S or NR¹², wherein R¹² is hydrogen, perhalomethyl, C₁₋₆-alkyl, aryl, arylalkyl, heteroarylalkyl, or acyl.

- In another preferred embodiment, the present invention is concerned with
20 compounds of formula I wherein Q is O or S.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Q is O.

- 25 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Ar represents arylene or heteroarylene, or a divalent heterocyclic group each of which can optionally be substituted with one or more halogen, C₁₋₆-alkyl or C₁₋₆-alkoxy.
- 30 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Ar represents arylene, or heteroarylene.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Ar represents arylene.

5 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁵ represents hydrogen, hydroxy, halogen, C₁₋₆-alkoxy, C₁₋₆-alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl or arylalkyl optionally substituted with one or more halogen, or perhalomethyl or R⁵ forms a bond together with R⁶.

10 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁵ represents hydrogen, halogen, C₁₋₆-alkoxy, C₁₋₆-alkyl, or perhalomethyl or R⁵ forms a bond together with R⁶.

15 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁵ represents hydrogen, halogen or R⁵ forms a bond together with R⁶.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁵ represents hydrogen.

20 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁶ represents hydrogen, C₁₋₆-alkoxy, C₁₋₆-alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, acyl or arylalkyl optionally substituted with one or more halogen or perhalomethyl or R⁶ forms a bond together with R⁵.

25 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁶ represents hydrogen, halogen, C₁₋₆-alkoxy, or R⁶ forms a bond together with R⁵.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁶ represents hydrogen, C₁₋₆-alkoxy, or R⁶ forms a bond together with R⁵.

30

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁶ represents hydrogen.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein M represents OR^7 , where R^7 represents hydrogen, C_{1-6} -alkyl, C_{4-6} -alkenynyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, aryl, arylalkyl, C_{1-6} -alkoxy C_{1-6} -alkyl, C_{1-6} -alkoxycarbonyl, aryloxy carbonyl, C_{1-6} -alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl or heteroarylalkyl groups optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein M represents OR^7 , where R^7 represents hydrogen, C_{1-6} -alkyl, C_{4-6} -alkenynyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, aryl, arylalkyl, C_{1-6} -alkoxy C_{1-6} -alkyl, heterocyclyl, heteroaryl or heteroarylalkyl groups optionally substituted with one or more halogen, or perhalomethyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein M represents OR^7 , where R^7 represents C_{1-6} -alkyl, or M represents $COYR^8$.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein M represents OR^7 , where R^7 represents ethyl, or M represents $COYR^8$.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^8 represents hydrogen, C_{1-6} alkyl, C_{4-6} -alkenynyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, aryl, arylalkyl, heterocyclyl, heteroaryl or heteroarylalkyl groups optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^8 represents hydrogen, C_{1-6} alkyl, C_{4-6} -alkenynyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, aryl, arylalkyl, heterocyclyl, heteroaryl or heteroarylalkyl groups optionally substituted with one or more halogen, or perhalomethyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^8 represents hydrogen or C_{1-6} alkyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^8 represents hydrogen, methyl or ethyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Y represents oxygen, sulphur or NR^{10} , where R^{10} represents hydrogen, C_{1-6} -alkyl, aryl, hydroxy C_{1-6} -alkyl or arylalkyl groups or when Y is NR^{10} , R^8 and R^{10} may form a 5 or 6 membered nitrogen containing ring, optionally substituted with one or more C_{1-6} -alkyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Y represents oxygen, or NR^{10} , where R^{10} represents hydrogen, C_{1-6} -alkyl, aryl, or arylalkyl groups, or when Y is NR^{10} , R^8 and R^{10} may form a 5 or 6 membered nitrogen containing ring, optionally substituted with one or more C_{1-6} -alkyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Y represents oxygen.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein k is an integer ranging from 1 to 2.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein n and m are 1.

Preferred compounds of the invention are:

- 2-Ethoxy-3-{4-[3-phenyl-3-(4-methylphenyl)-allyloxy]-phenyl}-propionic acid ethyl ester,
- 2-Ethoxy-3-{4-[3-phenyl-3-(4-methylphenyl)-allyloxy]-phenyl}-propionic acid,
- 3-{4-[3-(2-Chloro-phenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,
- 3-{4-[3-(2-Chloro-phenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid,
- 3-{4-[3,3-Bis-(4-methoxy-phenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,
- 3-{4-[3,3-Bis-(4-methoxy-phenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid,
- 3-{4-[3-Phenyl-3-(biphenyl-4-yl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,
- 3-{4-[3-Phenyl-3-(biphenyl-4-yl)-allyloxy]-phenyl}-2-ethoxy-propionic acid,
- 2-Ethoxy-3-{4-[3-phenyl-3-(thiophen-2-yl)-allyloxy]-phenyl}-propionic acid ethyl ester,
- 2-Ethoxy-3-{4-[3-phenyl-3-(thiophen-2-yl)-allyloxy]-phenyl}-propionic acid,
- 2-Ethoxy-3-{4-[3-phenyl-3-(pyridin-2-yl)-allyloxy]-phenyl}-propionic acid ethyl ester,
- 2-Ethoxy-3-{4-[3-phenyl-3-(pyridin-2-yl)-allyloxy]-phenyl}-propionic acid,

- 3-[4-(3, 3-Diphenyl-propoxy)-phenyl]-2-ethoxy-propionic acid ethyl ester,
 3-[4-(3,3-Diphenyl-propoxy)-phenyl]-2-ethoxy-propionic acid,
 2-Ethoxy-3-[4-[3-phenyl-3-(4-methylphenyl)-propoxy]-phenyl]-propionic acid ethyl ester,
 2-Ethoxy-3-[4-[3-phenyl-3-(4-methylphenyl)-propoxy]-phenyl]-propionic acid,
 5 3-[4-[3-Phenyl-3-(biphenyl-4-yl)-propoxy]-phenyl]-2-ethoxy-propionic acid ethyl ester,
 3-[4-[3-Phenyl-3-(biphenyl-4-yl)-propoxy]-phenyl]-2-ethoxy-propionic acid,
 2-[4-[3,3-Bis-(4-methoxy-phenyl)-allyloxy]-benzyl]-malonic acid dimethyl ester,
 (E)-(2S)-2-Ethoxy-3-[4-[3-(4-furan-2-yl-phenyl)-3-phenyl-allyloxy]-phenyl]-propionic acid ethyl ester,
 10 (E)-(2S)-2-Ethoxy-3-[4-[3-(4-furan-2-yl-phenyl)-3-phenyl-allyloxy]-phenyl]-propionic acid,
 (E)-(2S)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester,
 (E)-(2S)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid,
 (E, Z)-(2S)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester,
 15 (E, Z)-(2S)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid,
 3-[4-[3,3-Bis-(3-methyl-thiophen-2-yl)-allyloxy]-phenyl]-2-ethoxy-propionic acid ethyl ester,
 3-[4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl]-2-ethoxy-propionic acid ethyl ester,
 3-[4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl]-2-ethoxy-propionic acid,
 2-Ethoxy-3-[4-(3-phenyl-3-pyridin-4-yl-allyloxy)-phenyl]-propionic acid ethyl ester,
 20 2-Ethoxy-3-[4-(3-phenyl-3-pyridin-4-yl-allyloxy)-phenyl]-propionic acid,
 (E, Z)-(2S)-2-Ethoxy-3-[4-[3-(4-methoxyphenyl)-3-thiophen-2-yl-allyloxy]-phenyl]-propionic acid ethyl ester,
 (E, Z)-(2S)-2-Ethoxy-3-[4-[3-(4-methoxyphenyl)-3-thiophen-2-yl-allyloxy]-phenyl]-propionic acid,
 25 (E, Z)-(2S)-2-Ethoxy-3-[4-(3-phenyl-3-p-tolyl-allyloxy)-phenyl]-propionic acid ethyl ester,
 (E, Z)-(2S)-2-Ethoxy-3-[4-(3-phenyl-3-p-tolyl-allyloxy)-phenyl]-propionic acid,
 (2S)-3-[4-(3,3-Diphenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester,
 (2S)-3-[4-(3,3-Diphenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid,
 (Z)-(2S)-2-Ethoxy-3-[4-[3-(4-fluorophenyl)-3-phenyl-allyloxy]-phenyl]-propionic acid ethyl ester,
 30 ter,
 (Z)-(2S)-2-Ethoxy-3-[4-[3-(4-fluorophenyl)-3-phenyl-allyloxy]-phenyl]-propionic acid,
 (E)-(2S)-2-Ethoxy-3-[4-[3-(4-fluorophenyl)-3-phenyl-allyloxy]-phenyl]-propionic acid ethyl ester,
 (E)-(2S)-2-Ethoxy-3-[4-[3-(4-fluorophenyl)-3-phenyl-allyloxy]-phenyl]-propionic acid,

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- (2S)-3-{4-[3,3-Bis-(4-methoxyphenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,
 (2S)-3-{4-[3,3-Bis-(4-methoxyphenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid,
 (2S)-3-[4-(3,3-Di-p-tolyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester,
 (2S)-3-[4-(3,3-Di-p-tolyl-allyloxy)-phenyl]-2-ethoxy-propionic acid,
 5 (Z)-(2S)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid,
 (Z)-(2S)-3-{4-[3-(4-Bromophenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,
 (Z)-(2S)-3-{4-[3-(4-Bromophenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid,
 (2S)-3-[4-(3,3-Bis-biphenyl-4-yl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester,
 10 (2S)-3-[4-(3,3-Bis-biphenyl-4-yl-allyloxy)-phenyl]-2-ethoxy-propionic acid,
 (2S)-3-{4-[3,3-Bis-(4-bromophenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,
 (2S)-3-{4-[3,3-Bis-(4-bromophenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid,
 (Z)-(2S)-2-Ethoxy-3-{4-[3-(4-furan-2-yl-phenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid ethyl ester,
 15 (Z)-(2S)-2-Ethoxy-3-{4-[3-(4-furan-2-yl-phenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid,
 (E)-(2S)-3-{4-[3-(4-Bromophenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,
 (E)-(2S)-3-{4-[3-(4-Bromophenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid,
 (2S)-3-{4-[3,3-Bis-(4-furan-2-yl-phenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,
 20 (2S)-3-{4-[3,3-Bis-(4-furan-2-yl-phenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid,
 (E, Z)-(2S)-3-[4-(3-Biphenyl-4-yl-3-p-tolyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester,
 (E, Z)-(2S)-3-[4-(3-Biphenyl-4-yl-3-p-tolyl-allyloxy)-phenyl]-2-ethoxy-propionic acid, and
 (E, Z)-(2R)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester;
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or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

- 30 In the above structural formulas and throughout the present specification, the following terms have the indicated meaning:

The term "C_{1-n}-alkyl" wherein n' can be from 2 through 12, as used herein, represents a branched or straight or cyclic alkyl group having from one to the specified number of carbon
 35 atoms. Examples of such groups include, but are not limited to methyl, ethyl, n-propyl, iso-

10 The terms "C_{2-n'}-alkynyl" wherein n' can be from 3 through 15, as used herein, represents an unsaturated branched or straight hydrocarbon group having from 2 to the specified number of carbon atoms and at least one triple bond. Examples of such groups include, but are not limited to, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl and the like.

20 The term "C₁₋₁₂-alkoxy" as used herein, alone or in combination is intended to include those C₁₋₁₂-alkyl groups of the designated length in either a linear or branched or cyclic configuration linked through an ether oxygen having its free valence bond from the ether oxygen. Examples of linear alkoxy groups are methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy and the like.

25 Examples of branched alkoxy are isopropoxy, sec-butoxy, tert-butoxy, isopentoxy, isohexoxy and the like. Examples of cyclic alkoxy are cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and the like.

The term "C₁₋₁₂-alkylthio" as used herein, alone or in combination, refers to a straight or branched or cyclic monovalent substituent comprising a C₁₋₁₂-alkyl group linked through a divalent sulfur atom having its free valence bond from the sulfur atom and having 1 to 12 carbon atoms e.g. methylthio, ethylthio, propylthio, butylthio, pentylthio and the like. Examples of cyclic alkylthio are cyclopropylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio and the like.

The term "C₁₋₁₂-alkylamino" as used herein, alone or in combination, refers to a straight or branched or cyclic monovalent substituent comprising a C₁₋₁₂-alkyl group linked through amino having a free valence bond from the nitrogen atom e.g. methylamino, ethylamino, propylamino, butylamino, pentylamino and the like. Examples of cyclic alkylamino are cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclohexylamino and the like.

The term "hydroxyC₁₋₁₂-alkyl" as used herein, alone or in combination, refers to a C₁₋₁₂-alkyl as defined herein whereto is attached a hydroxy group, e.g. hydroxyethyl, 1-hydroxypropyl, 2-hydroxypropyl and the like.

The term "arylamino" as used herein, alone or in combination, refers to an aryl as defined herein linked through amino having a free valence bond from the nitrogen atom, e.g., phenylamino, naphthylamino and the like.

The term "arylalkylamino" as used herein, alone or in combination, refers to an arylalkyl as defined herein linked through amino having a free valence bond from the nitrogen atom, e.g., benzylamino, phenethylamino, 3-phenylpropylamino, 1-naphthylmethylamino, 2-(1-naphthyl)ethylamino and the like.

The term "aminoC₁₋₁₂-alkyl" as used herein, alone or in combination, refers to a C₁₋₁₂-alkyl as defined herein whereto is attached an amino group, e.g., aminoethyl, 1-aminopropyl, 2-aminopropyl and the like.

The term "aryloxy carbonyl" as used herein, alone or in combination, refers to an aryloxy as defined herein linked through a carbonyl having a free valence bond from the carbon atom, e.g., phenoxycarbonyl, 1-naphthyloxycarbonyl or 2-naphthyloxycarbonyl and the like.

The term "arylalkoxy carbonyl" as used herein, alone or in combination, refers to an arylalkoxy as defined herein linked through a carbonyl having a free valence bond from the carbon atom, e.g., benzyloxycarbonyl, phenethoxycarbonyl, 3-phenylpropoxycarbonyl, 1-naphthylmethoxycarbonyl, 2-(1-naphthyl)ethoxycarbonyl and the like.

The term "C₁₋₁₂-alkoxyC₁₋₁₂-alkyl" as used herein, alone or in combination, refers to a C₁₋₁₂-alkyl as defined herein whereto is attached a C₁₋₁₂-alkoxy as defined herein, e.g., methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl and the like.

- 5 The term "aryloxyC₁₋₁₂-alkyl" as used herein, alone or in combination, refers to a C₁₋₁₂-alkyl as defined herein whereto is attached an aryloxy as defined herein, e.g., phenoxymethyl, phenoxydodecyl, 1-naphthyloxyethyl, 2-naphthyloxypropyl and the like.

- 10 The term "arylalkoxyC₁₋₁₂-alkyl" as used herein, alone or in combination, refers to a C₁₋₁₂-alkyl as defined herein whereto is attached an arylalkoxy as defined herein, e.g., benzyloxymethyl, phenethoxydodecyl, 3-phenylpropoxyethyl, 1-naphthylmethoxypropyl, 2-(1-naphthyl)ethoxymethyl and the like.

- 15 The term "thioC₁₋₁₂-alkyl" as used herein, alone or in combination, refers to a C₁₋₁₂-alkyl as defined herein whereto is attached a group of formula -SR^{'''} wherein R^{'''} is hydrogen, C₁₋₆-alkyl or aryl, e.g., thiomethyl, methylthiomethyl, phenylthioethyl and the like.

- 20 The term "C₁₋₁₂-alkoxycarbonylamino" as used herein, alone or in combination, refers to a C₁₋₁₂-alkoxycarbonyl as defined herein linked through amino having a free valence bond from the nitrogen atom, e.g., methoxycarbonylamino, carbethoxyamino, propoxycarbonylamino, isopropoxycarbonylamino, n-butoxycarbonylamino, tert-butoxycarbonylamino and the like.

- 25 The term "aryloxycarbonylamino" as used herein, alone or in combination, refers to an aryloxycarbonyl as defined herein linked through amino having a free valence bond from the nitrogen atom, e.g., phenoxycarbonylamino, 1-naphthyloxycarbonylamino or 2-naphthyloxycarbonylamino and the like.

- 30 The term "arylalkoxycarbonylamino" as used herein, alone or in combination, refers to an arylalkoxycarbonyl as defined herein linked through amino having a free valence bond from the nitrogen atom, e.g., benzyloxycarbonylamino, phenethoxycarbonylamino, 3-phenylpropoxycarbonylamino, 1-naphthylmethoxycarbonylamino, 2-(1-naphthyl)ethoxycarbonylamino and the like.

5 The term "arylene" is intended to include divalent aromatic rings, such as carboxylic aromatic rings selected from the group consisting of phenylene, naphthylene and the like optionally substituted with halogen, amino, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy and the like.

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The term "C₁₋₆-dialkylamino" as used herein refers to an amino group wherein the two hydrogen atoms independently are substituted with a straight or branched, saturated hydrocarbon chain having the indicated number of carbon atoms; such as dimethylamino, N-ethyl-N-methylamino, diethylamino, dipropylamino, N-(n-butyl)-N-methylamino, di(n-pentyl)amino and the like.

The term "acyloxy" as used herein refers to acyl as defined herein linked to an oxygen atom having its free valence bond from the oxygen atom, e.g., acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, pivaloyloxy, valeryloxy and the like.

The term "C₁₋₁₂-alkoxycarbonyl" as used herein refers to a monovalent substituent comprising a C₁₋₁₂-alkoxy group linked through a carbonyl group; such as, e.g., methoxycarbonyl, carbethoxy, propoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, 3-methylbutoxycarbonyl, n-hexoxycarbonyl and the like.

The term "heteroaryl" as used herein, alone or in combination, refers to a monovalent substituent comprising a 5-6 membered monocyclic aromatic system or a 9-10 membered bicyclic aromatic system containing one or more heteroatoms selected from nitrogen, oxygen and sulfur, e.g., furan, thiophene, pyrrole, imidazole, pyrazole, triazole, pyridine, pyrazine, pyrimidine, pyridazine, isothiazole, isoxazole, oxazole, oxadiazole, thiadiazole, quinoline, isoquinoline, quinazoline, quinoxaline, indole, benzimidazole, benzofuran, pteridine and purine and the like.

The term "heteroarylene" as used herein, alone or in combination, refers to a divalent group comprising a 5-6 membered monocyclic aromatic system or a 9-10 membered bicyclic aromatic system containing one or more heteroatoms selected from nitrogen, oxygen and sulfur, e.g., furan, thiophene, pyrrole, imidazole, pyrazole, triazole, pyridine, pyrazine, pyrimidine, pyridazine, isothiazole, isoxazole, oxazole, oxadiazole, thiadiazole, quinoline, isoquinoline, quinazoline, quinoxaline, indole, benzimidazole, benzofuran, pteridine and purine and the like.

The term "heteroaryloxy" as used herein, alone or in combination, refers to a heteroaryl as defined herein linked to an oxygen atom having its free valence bond from the oxygen atom e.g. pyrrole, imidazole, pyrazole, triazole, pyridine, pyrazine, pyrimidine, pyridazine, isothiazole, isoxazole, oxazole, oxadiazole, thiadiazole, quinoline, isoquinoline, quinazoline, quinoxaline, indole, benzimidazole, benzofuran, pteridine and purine linked to oxygen, and the like.

The term "arylalkyl" as used herein refers to a straight or branched saturated carbon chain containing from 1 to 6 carbons substituted with an aromatic carbohydride; such as benzyl, phenethyl, 3-phenylpropyl, 1-naphthylmethyl, 2-(1-naphthyl)ethyl and the like.

The term "aryloxy" as used herein refers to phenoxy, 1-naphthyloxy, 2-naphthyloxy and the like.

The term "arylalkoxy" as used herein refers to a C₁₋₆-alkoxy group substituted with an aromatic carbohydride, such as benzyloxy, phenethoxy, 3-phenylpropoxy, 1-naphthylmethoxy, 2-(1-naphthyl)ethoxy and the like.

The term "heteroarylalkyl" as used herein refers to a straight or branched saturated carbon chain containing from 1 to 6 carbons substituted with a heteroaryl group, such as (2-furyl)methyl, (3-furyl)methyl, (2-thienyl)methyl, (3-thienyl)methyl, (2-pyridyl)methyl, 1-methyl-1-(2-pyrimidyl)ethyl and the like.

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The term "heteroarylalkoxy" as used herein refers to a heteroarylalkyl as defined herein linked to an oxygen atom having its free valence bond from the oxygen atom, e.g., (2-furyl)methyl, (3-furyl)methyl, (2-thienyl)methyl, (3-thienyl)methyl, (2-pyridyl)methyl, 1-methyl-1-(2-pyrimidyl)ethyl linked to oxygen, and the like.

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The term "acylamino" as used herein refers to an amino group wherein one of the hydrogen atoms is substituted with an acyl group, such as, e.g., acetamido, propionamido, isopropylcarbonylamino and the like.

15 The term "(C₃₋₆-cycloalkyl)C₁₋₆-alkyl" as used herein, alone or in combination, refers to a straight
or branched, saturated hydrocarbon chain having 1 to 6 carbon atoms and being monosubsti-
tuted with a C₃₋₆-cycloalkyl group, the cycloalkyl group optionally being mono- or polysubsti-
tuted with C₁₋₆-alkyl, halogen, hydroxy or C₁₋₆-alkoxy; such as, e.g., cyclopropylmethyl, (1-
methylcyclopropyl)methyl, 1-(cyclopropyl)ethyl, cyclopentylmethyl, cyclohexylmethyl and the
20 like.

The term "arylthio" as used herein, alone or in combination, refers to an aryl group linked through a divalent sulfur atom having its free valence bond from the sulfur atom, the aryl group optionally being mono- or polysubstituted with C₁₋₆-alkyl, halogen, hydroxy or C₁₋₆-alkoxy; e.g., phenylthio, (4-methylphenyl)- thio, (2-chlorophenyl)thio and the like.

The term "C₁₋₆-alkylaminocarbonyl" as used herein refers to a monovalent substituent comprising a C₁₋₆-monoalkylamino group linked through a carbonyl group such as, e.g., methylaminocarbonyl, ethylaminocarbonyl, n-propylaminocarbonyl, isopropylaminocarbonyl, n-butylaminocarbonyl, sec-butylaminocarbonyl, isobutylaminocarbonyl, tert-butylaminocarbonyl, n-pentylaminocarbonyl, 2-methylbutylaminocarbonyl, 3-methylbutylaminocarbonyl, n-hexylaminocarbonyl, 4-methylpentylaminocarbonyl, neopentylaminocarbonyl, n-hexylaminocarbonyl and 2,2-dimethylpropylaminocarbonyl and the like.

As used herein, the phrase "heterocyclyl" means a monovalent saturated or unsaturated non aromatic group being monocyclic and containing one or more, such as from one to four carbon atom(s), and from one to four N, O or S atom(s) or a combination thereof. The phrase "heterocyclyl" includes, but is not limited to, 5-membered heterocycles having one hetero atom (e.g. pyrrolidine, pyrroline and the like); 5-membered heterocycles having two heteroatoms in 1,2 or 1,3 positions (e.g. pyrazoline, pyrazolidine, 1,2-oxathiolane, imidazolidine, imidazoline, 4-oxazolone and the like); 5-membered heterocycles having three heteroatoms (e.g. tetrahydrofuran and the like); 5-membered heterocycles having four heteroatoms; 6-membered heterocycles with one heteroatom (e.g., piperidine and the like); 6-membered heterocycles with two heteroatoms (e.g., piperazine, morpholine and the like); 6-membered heterocycles with three heteroatoms; and 6-membered heterocycles with four heteroatoms, and the like.

As used herein, the phrase "a divalent heterocyclic group" means a divalent saturated or unsaturated system being monocyclic and containing one or more, such as from one to four carbon atom(s), and one to four N, O or S atom(s) or a combination thereof. The phrase a divalent heterocyclic group includes, but is not limited to, 5-membered heterocycles having one hetero atom (e.g., pyrrolidine, pyrroline and the like); 5-membered heterocycles having two heteroatoms in 1,2 or 1,3 positions (e.g. pyrazoline, pyrazolidine, 1,2-oxathiolane, imidazolidine, imidazoline, 4-oxazolone and the like); 5-membered heterocycles having three heteroatoms (e.g. tetrahydrofuran and the like); 5-membered heterocycles having four heteroatoms; 6-membered heterocycles with one heteroatom (e.g. piperidine and the like); 6-membered heterocycles with two heteroatoms (e.g. piperazine, morpholine and the like); 6-membered heterocycles with three heteroatoms; and 6-membered heterocycles with four heteroatoms, and the like.

As used herein, the phrase "a 5-6 membered cyclic ring" means an unsaturated or saturated or aromatic system containing one or more carbon atoms and optionally from one to four N, O or S atom(s) or a combination thereof. The phrase "a 5-6 membered cyclic ring" includes, but is not limited to, e.g. cyclopentyl, cyclohexyl, phenyl, cyclohexenyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, pyrrolyl, 2H-pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, morpholinyl, thiomorpholinyl, isothiazolyl, isoxazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, 1,3-dioxolanyl, 1,4-dioxolanyl and the like, 5-membered heterocycles having one hetero atom (e.g.,

thiophenes, pyrroles, furans and the like); 5-membered heterocycles having two heteroatoms in 1,2 or 1,3 positions (e.g. oxazoles, pyrazoles, imidazoles, thiazoles, purines and the like); 5-membered heterocycles having three heteroatoms (e.g., triazoles, thiadiazoles and the like); 5-membered heterocycles having four heteroatoms; 6-membered heterocycles with one heteroatom (e.g. pyridine, quinoline, isoquinoline, phenanthridine, cyclohepta[b]pyridine and the like); 6-membered heterocycles with two heteroatoms (e.g. pyridazines, cinnolines, phthalazines, pyrazines, pyrimidines, quinazolines, morpholines and the like); 6-membered heterocycles with three heteroatoms (e.g., 1,3,5-triazine and the like); and 6-membered heterocycles with four heteroatoms and the like.

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As used herein, the phrase "a 9-10 membered bicyclic ring" means an unsaturated or saturated or aromatic system containing one or more carbon atoms and optionally from one to four N, O or S atom(s) or a combination thereof. The phrase "a 9-10 membered bicyclic ring" includes but is not limited to naphthalene, quinoline, isoquinoline, indole,

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benzothiophene, benzofuran and the like.

Certain of the above defined terms may occur more than once in the above formula (I), and upon such occurrence each term shall be defined independently of the other.

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The present invention also encompasses pharmaceutically acceptable salts of the present compounds. Such salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable base addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts. Acid addition salts include salts of inorganic acids as well as organic acids. Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, nitric acids and the like. Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, lactic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methanesulfonic, ethanesulfonic, tartaric, ascorbic, pantoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic,

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EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic acids, sulfates, nitrates, phosphates, perchlorates, borates, acetates, benzoates, hydroxynaphthoates, glycerophosphates, ketoglutarates and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in J. Pharm. Sci. 1977, 66, 2, which is incorporated herein by reference. Exam-

ples of metal salts include lithium, sodium, potassium, magnesium salts and the like. Examples of ammonium and alkylated ammonium salts include ammonium, methylammonium, dimethylammonium, trimethylammonium, ethylammonium, hydroxyethylammonium, diethylammonium, butylammonium, tetramethylammonium salts and the like. Examples of organic bases include lysine, arginine, guanidine, diethanolamine, choline and the like.

The pharmaceutically acceptable salts are prepared by reacting the compound of formula I with 1 to 4 equivalents of a base such as sodium hydroxide, sodium methoxide, sodium hydride, potassium t-butoxide, calcium hydroxide, magnesium hydroxide and the like, in solvents like ether, THF, methanol, t-butanol, dioxane, isopropanol, ethanol etc. Mixture of solvents may be used. Organic bases like lysine, arginine, diethanolamine, choline, guanidine and their derivatives etc. may also be used. Alternatively, acid addition salts wherever applicable are prepared by treatment with acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, p-toluenesulphonic acid, methanesulfonic acid, acetic acid, citric acid, maleic acid, salicylic acid, hydroxynaphthoic acid, ascorbic acid, palmitic acid, succinic acid, benzoic acid, benzenesulfonic acid, tartaric acid and the like in solvents like ethyl acetate, ether, alcohols, acetone, THF, dioxane etc. Mixture of solvents may also be used.

The stereoisomers of the compounds forming part of this invention may be prepared by using reactants in their single enantiomeric form in the process wherever possible or by conducting the reaction in the presence of reagents or catalysts in their single enantiomer form or by resolving the mixture of stereoisomers by conventional methods. Some of the preferred methods include use of microbial resolution, resolving the diastereomeric salts formed with chiral acids such as mandelic acid, camphorsulfonic acid, tartaric acid, lactic acid, and the like wherever applicable or chiral bases such as brucine, cinchona alkaloids and their derivatives and the like. Commonly used methods are compiled by Jaques et al in "Enantiomers, Racemates and Resolution" (Wiley Interscience, 1981). More specifically the compound of formula I may be converted to a 1:1 mixture of diastereomeric amides by treating with chiral amines, amino acids, amino alcohols derived from amino acids; conventional reaction conditions may be employed to convert acid into an amide; the diastereomers may be separated either by fractional crystallization or chromatography and the stereoisomers of compound of formula I may be prepared by hydrolysing the pure diastereomeric amide.

Various polymorphs of compound of general formula I forming part of this invention may be prepared by crystallization of compound of formula I under different conditions. For example, using different solvents commonly used or their mixtures for recrystallization; crystallizations at different temperatures; various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe NMR spectroscopy, ir spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques.

The invention also encompasses prodrugs of the present compounds, which on administration undergo chemical conversion by metabolic processes before becoming active pharmacological substances. In general, such prodrugs will be functional derivatives of the present compounds, which are readily convertible *in vivo* into the required compound of the formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The invention also encompasses active metabolites of the present compounds.

Furthermore, the present compounds of formula I can be utilized in the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR).

In a further aspect, the present invention relates to a method of treating and/or preventing Type I or Type II diabetes.

In a still further aspect, the present invention relates to the use of one or more compounds of formula I or pharmaceutically acceptable salts thereof for the preparation of a medicament for the treatment and/or prevention of Type I or Type II diabetes.

In a still further aspect, the present compounds are useful for the treatment and/or prevention of IGT.

In a still further aspect, the present compounds are useful for the treatment and/or prevention of Type 2 diabetes.

5 In a still further aspect, the present compounds are useful for the delaying or prevention of the progression from non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes.

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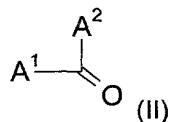
The invention also relates to pharmaceutical compositions comprising, as an active ingredient, at least one compound of the formula I or any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof together with one or more pharmaceutically acceptable carriers or diluents.

Furthermore, the invention relates to the use of compounds of formula I or their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts or pharmaceutically acceptable solvates thereof for the preparation of a pharmaceutical composition for the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR) such as the conditions mentioned above.

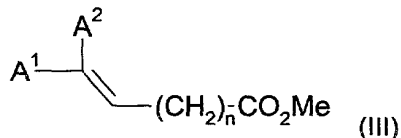
The present invention also relates to a process for the preparation of the above said novel compounds, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts or pharmaceutically acceptable solvates.

The method comprises:

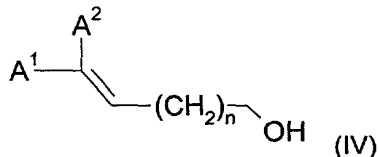
- a) Reacting a compound of formula (II) where A¹ and A² are as defined previously with a phosphonate ester in a Horner Emmons reaction



to give a compound of formula III where A¹ and A² and n are as defined previously,



whereupon a compound of formula III can be reduced with diisobutyl aluminium hydride to give a compound of formula IV where A¹ and A² and n are as defined previously. Alternatively a compound of formula IV can be prepared via reaction of a compound of formula II with (Ph₃P)₃PCH₂(CH₂)_nCH₂OH.Br and BuLi in a Wittig reaction



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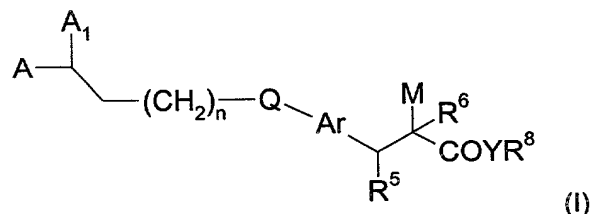


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A compound of formula VI can undergo a Mitsunobo reaction with a compound of formula V to give a compound of formula I, wherein k=2 and A¹, A², Q, Ar, M, Y, n and R⁵-R⁸ are as defined previously.



Ester deprotection of a compound of formula (I) can be carried out using standard hydrolysis techniques, to give a compound of formula I, wherein Y is O, k=2 and A¹, A², Q, Ar, M, n and R⁵-R⁸ are as defined previously.

5

PHARMACOLOGICAL METHODS

In vitro PPAR alpha and PPAR gamma activation activity.

10 Principle

The PPAR gene transcription activation assays were based on transient transfection into human HEK293 cells of two plasmids encoding a chimeric test protein and a reporter protein respectively. The chimeric test protein was a fusion of the DNA binding domain (DBD) from the yeast GAL4 transcription factor to the ligand binding domain (LBD) of the human PPAR proteins. The PPAR LBD harbored in addition to the ligand binding pocket also the native activation domain (activating function 2 = AF2) allowing the fusion protein to function as a PPAR ligand dependent transcription factor. The GAL4 DBD will force the fusion protein to bind only to Gal4 enhancers (of which none existed in HEK293 cells). The reporter plasmid contained a Gal4 enhancer driving the expression of the firefly luciferase protein. After transfection, HEK293 cells expressed the GAL4-DBD-PPAR-LBD fusion protein. The fusion protein will in turn bind to the Gal4 enhancer controlling the luciferase expression, and do nothing in the absence of ligand. Upon addition to the cells of a PPAR ligand, luciferase protein will be produced in amounts corresponding to the activation of the PPAR protein. The amount of luciferase protein is measured by light emission after addition of the appropriate substrate.

30

Methods

Cell culture and transfection: HEK293 cells were grown in DMEM + 10% FCS, 1% PS. Cells were seeded in 96-well plates the day before transfection to give a confluency of 80 % at
5 transfection. 0,8 µg DNA per well was transfected using FuGene transfection reagent according to the manufacturers instructions (Boehringer-Mannheim). Cells were allowed to express protein for 48 h followed by addition of compound.

Plasmids: Human PPAR α and γ was obtained by PCR amplification using cDNA templates
10 from liver, intestine and adipose tissue respectively. Amplified cDNAs were cloned into pCR2.1 and sequenced. The LBD from each isoform PPAR was generated by PCR (PPAR α : aa 167 - C-term; PPAR γ : aa 165 - C-term) and fused to GAL4-DBD by subcloning fragments in frame into the vector pM1 generating the plasmids pM1 α LBD and pM1 γ LBD. Ensuing fusions were verified by sequencing. The reporter was constructed by inserting an
15 oligonucleotide encoding five repeats of the Gal4 recognition sequence into the pGL2 vector (Promega).

Compounds: All compounds were dissolved in DMSO and diluted 1:1000 upon addition to the cells. Cells were treated with compound (1:1000 in 200 µl growth medium including de-
20 lipidated serum) for 24 h followed by luciferase assay.

Luciferase assay: Medium including test compound was aspirated and 100 µl PBS incl. 1mM Mg++ and Ca++ was added to each well. The luciferase assay was performed using the LucLite kit according to the manufacturers instructions (Packard Instruments). Light emission
25 was quantified by counting SPC mode on a Packard Instruments top-counter.

PHARMACEUTICAL COMPOSITIONS

30 In another aspect, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, an effective amount of at least one of the compounds of formula I or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

The present compounds may also be administered in combination with one or more further pharmacologically active substances, e.g., selected from antiobesity agents, antidiabetics, antihypertensive agents, agents for the treatment and/or prevention of complications resulting from or associated with diabetes and agents for the treatment and/or prevention of complications and disorders resulting from or associated with obesity.

Thus, in a further aspect of the invention the present compounds may be administered in combination with one or more antiobesity agents or appetite regulating agents.

Such agents may be selected from the group consisting of CART (cocaine amphetamine regulated transcript) agonists, NPY (neuropeptide Y) antagonists, MC4 (melanocortin 4) agonists, orexin antagonists, TNF (tumor necrosis factor) agonists, CRF (corticotropin releasing factor) agonists, CRF BP (corticotropin releasing factor binding protein) antagonists, urocortin agonists, $\beta 3$ agonists, MSH (melanocyte-stimulating hormone) agonists, MCH (melanocyte-concentrating hormone) antagonists, CCK (cholecystokinin) agonists, serotonin re-uptake inhibitors, serotonin and noradrenaline re-uptake inhibitors, mixed serotonin and noradrenergic compounds, 5HT (serotonin) agonists, bombesin agonists, galanin antagonists, growth hormone, growth hormone releasing compounds, TRH (thyrotropin releasing hormone) agonists, UCP 2 or 3 (uncoupling protein 2 or 3) modulators, leptin agonists, DA agonists (bromocriptin, doprexin), lipase/amylase inhibitors, RXR (retinoid X receptor) modulators or TR β agonists.

In one embodiment of the invention the antiobesity agent is leptin.

In another embodiment the antiobesity agent is dexamphetamine or amphetamine.

In another embodiment the antiobesity agent is fenfluramine or dexfenfluramine.

In still another embodiment the antiobesity agent is sibutramine.

In a further embodiment the antiobesity agent is orlistat.

In another embodiment the antiobesity agent is mazindol or phentermine.

Suitable antidiabetics comprise insulin, GLP-1 (glucagon like peptide-1) derivatives such as those disclosed in WO 98/08871 to Novo Nordisk A/S, which is incorporated herein by reference as well as orally active hypoglycemic agents.

- 5 The orally active hypoglycemic agents preferably comprise sulphonylureas, biguanides, meglitinides, glucosidase inhibitors, glucagon antagonists such as those disclosed in WO 99/01423 to Novo Nordisk A/S and Agouron Pharmaceuticals, Inc., GLP-1 agonists, potassium channel openers such as those disclosed in WO 97/26265 and WO 99/03861 to Novo Nordisk A/S which are incorporated herein by reference, DPP-IV (dipeptidyl peptidase-IV)
- 10 inhibitors, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis and/or glycogenolysis, glucose uptake modulators, compounds modifying the lipid metabolism such as antihyperlipidemic agents and antilipidemic agents as HMG CoA inhibitors (statins), compounds lowering food intake, RXR agonists and agents acting on the ATP-dependent potassium channel of the β -cells.

- 15 In one embodiment of the invention the present compounds are administered in combination with insulin.

- In a further embodiment the present compounds are administered in combination with a sulphonylurea, e.g., tolbutamide, glibenclamide, glipizide or glicazide.
- 20

In another embodiment the present compounds are administered in combination with a biguanide, e.g., metformin.

- 25 In yet another embodiment the present compounds are administered in combination with a meglitinide, e.g., repaglinide.

In a further embodiment the present compounds are administered in combination with an α -glucosidase inhibitor, e.g., miglitol or acarbose.

- 30 In another embodiment the present compounds are administered in combination with an agent acting on the ATP-dependent potassium channel of the β -cells, e.g., tolbutamide, glibenclamide, glipizide, glicazide or repaglinide.

Furthermore, the present compounds may be administered in combination with nateglinide.

In still another embodiment the present compounds are administered in combination with an antihyperlipidemic agent or antilipidemic agent, e.g., cholestyramine, colestipol, clofibrate,
5 gemfibrozil, lovastatin, pravastatin, simvastatin, probucol or dextrothyroxine.

In a further embodiment the present compounds are administered in combination with more than one of the above-mentioned compounds, e.g., in combination with a sulphonylurea and metformin, a sulphonylurea and acarbose, repaglinide and metformin, insulin and a sulphonylurea, insulin and metformin, insulin, insulin and lovastatin, etc.
10

Furthermore, the present compounds may be administered in combination with one or more antihypertensive agents. Examples of antihypertensive agents are β -blockers such as alprenolol, atenolol, timolol, pindolol, propranolol and metoprolol, ACE (angiotensin converting
15 enzyme) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, quinapril and ramipril, calcium channel blockers such as nifedipine, felodipine, nicardipine, isradipine, nimodipine, diltiazem and verapamil, and α -blockers such as doxazosin, urapidil, prazosin and terazosin. Further reference can be made to Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

20 It should be understood that any suitable combination of the compounds according to the invention with one or more of the above-mentioned compounds and optionally one or more further pharmacologically active substances are considered to be within the scope of the present invention.

25 Pharmaceutical compositions containing a compound of the present invention may be prepared by conventional techniques, e.g., as described in Remington: The Science and Practise of Pharmacy, 19th Ed., 1995. The compositions may appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

30 Typical compositions include a compound of formula I or a pharmaceutically acceptable acid addition salt thereof, associated with a pharmaceutically acceptable excipient which may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container. In making the compositions,

- conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatine, lactose, terra alba, sucrose, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavouring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.
- The pharmaceutical compositions can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or colouring substances and the like, which do not deleteriously react with the active compounds.

- The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral, nasal, pulmonary, transdermal or parenteral, e.g., rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment, the oral route being preferred.

- If a solid carrier is used for oral administration, the preparation may be tableted, placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

For nasal administration, the preparation may contain a compound of formula I dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, e.g., propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabens.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet which may be prepared by conventional tableting techniques may contain:

Core:

Active compound (as free compound or salt thereof)	5 mg
Colloidal silicon dioxide (AEROSIL)	1.5 mg
Cellulose, microcryst. (AVICEL)	70 mg
Modified cellulose gum (AC-DI-SOL)	7.5 mg
Magnesium stearate	Ad.

Coating:

HPMC approx.	9 mg
*Mywacett 9-40 T approx.	0.9 mg

*Acylated monoglyceride used as plasticizer for film coating.

The compounds of the invention may be administered to a mammal, especially a human in need of such treatment, prevention, elimination, alleviation or amelioration of diseases related to the regulation of blood sugar. Such mammals include also animals, both domestic animals, e.g., household pets, and non-domestic animals such as wildlife.

The compounds of the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.05 to about 100 mg, preferably from about 0.1 to about 100 mg, per day may be used. A most preferable dosage is about 0.1 mg to about 70 mg per day. In choosing a regimen for patients it may frequently be necessary to
5 begin with a dosage of from about 2 to about 70 mg per day and when the condition is under control to reduce the dosage as low as from about 0.1 to about 10 mg per day. The exact dosage will depend upon the mode of administration, on the therapy desired, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

10

Generally, the compounds of the present invention are dispensed in unit dosage form comprising from about 0.1 to about 100 mg of active ingredient together with a pharmaceutically acceptable carrier per unit dosage.

15 Usually, dosage forms suitable for oral, nasal, pulmonary or transdermal administration comprise from about 0.001 mg to about 100 mg, preferably from about 0.01 mg to about 50 mg of the compounds of formula I admixed with a pharmaceutically acceptable carrier or diluent.

20 Any novel feature or combination of features described herein is considered essential to this invention.

EXAMPLES

25 The process for preparing compounds of formula I, and preparations containing them, is further illustrated in the following examples, which however, are not to be construed as limiting.

The structures of the compounds are confirmed by either elemental analysis (MA) nuclear magnetic resonance (NMR) or mass spectrometry (MS). NMR shifts (δ) are given in parts per million (ppm) and only selected peaks are given. mp is melting point and is given in $^{\circ}\text{C}$.
30 Column chromatography was carried out using the technique described by W.C. Still et al, J. Org. Chem. 1978, 43, 2923-2925 on Merck silica gel 60 (Art 9385). Compounds used as starting materials are either known compounds or compounds which can readily be prepared by methods known per se.

Abbreviations:

TLC: thin layer chromatography

DMSO: dimethylsulfoxide

5 CDCl₃: deuterated chloroform

DMF: N,N-dimethylformamide

min: minutes

h: hours

10

Example 1(E,Z)-2-Ethoxy-3-{4-[3-phenyl-3-(4-methylphenyl)-allyloxy]-phenyl}-propionic acid ethyl ester

15 To a solution of 3-phenyl-3-(4-methyl-phenyl)-prop-2-en-1-ol (150mg, 0.6mmol), triphenyl-phosphine (195mg, 0.73mmol) and 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (190mg, 0.79mmol) in THF at ice bath temperature was added diethylazodicarboxylate (0.11mL, 0.73mmol) and the reaction stirred 1.5h at this temperature and 16h at room temperature. Ice water was added and the crude product isolated by a dichloromethane extrac-

20 tion and brine wash. Concentration under reduced pressure and flash chromatography gave the title compound (300mg).

¹H NMR (CDCl₃, 300 MHz); δ 1.07-1.28 (6H, 2xCH₃), 2.30 and 2.40 (3H, CH₃), 2.90-2.93 (2H, CH₂), 3.30-3.40 and 3.51-3.61 (2H, OCH₂), 3.90-4.0 (1H, CHCO₂), 4.10-4.19 (2H, OCH₂), 4.41-4.61 (2H, OCH₂) 6.23-6.32 (1H, CHalkene), 6.70-6.81 (2H, aryl), 7.03-7.45 (remaining H, aryl).

25

MS calcd for C₂₉H₃₂O₄ 444.6, Found 444.2Example 2

30

(E,Z)-2-Ethoxy-3-{4-[3-phenyl-3-(4-methylphenyl)-allyloxy]-phenyl}-propionic acid

(E,Z)-2-Ethoxy-3-{4-[3-phenyl-3-(4-methylphenyl)-allyloxy]-phenyl}-propionic acid ethyl ester (example 1) (80mg, 0.18mmol) was hydrolyzed in 1N NaOH (0.35mL) and ethanol (0.35mL)

for 4 h at room temperature and 16h at 5°C. Water (1mL) was added and the reaction mixture was neutralised with 6N HCl. The crude product was extracted with dichloromethane and concentrated under reduced pressure. Flash chromatography gave the title compound (48mg).

5

^1H NMR (CDCl_3 , 300 MHz); δ 1.07-1.20 (3H, CH_3), 2.32 and 2.40 (3H, CH_3), 2.85-3.10 (2H, CH_2), 3.30-3.45 and 3.51-3.68 (2H, OCH_2), 3.95-4.06 (1H, CHCO_2), 4.51-4.61 (2H, OCH_2) 6.21-6.41 (1H, CHalkene), 6.72-6.82 (2H, aryl), 7.03-7.50 (remaining H, aryl).
MS calcd for $\text{C}_{27}\text{H}_{28}\text{O}_4$ 416.5, Found 416.3.

10

Example 3

(E, Z)-3-{4-[3-(2-Chloro-phenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester

15

To a solution of 3-(2-chloro-phenyl)-3-phenyl-prop-2-en-1-ol (370mg, 1.5mmol), tributylphosphine (0.5mL, 1.6mmol) and 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (380mg, 1.6mmol) in benzene at ice bath temperature was added azodicarboxylic dipiperidide (403mg, 1.6mmol) and the reaction stirred 1h. Work up and purification as for Example 1 gave the title compound (490mg).

20

^1H NMR (CDCl_3 , 300 MHz); δ 1.07-1.30 (6H, $2\times\text{CH}_3$), 2.90-2.95 (2H, CH_2), 3.29-3.40 and 3.52-3.63 (2H, OCH_2), 3.90-4.0 (1H, CHCO_2), 4.10-4.20 (2H, OCH_2), 4.35-4.56 and 4.70-4.80 (2H, OCH_2), 6.00-6.08 and 6.42-6.53 (1H, CHalkene), 6.70-6.81 (2H, aryl), 7.06-7.55 (remaining H, aryl).

25

MS calcd for $\text{C}_{28}\text{H}_{29}\text{ClO}_4$ 465.0, Found 464.2.

Example 4

30 (E, Z)-3-{4-[3-(2-Chloro-phenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid

(E, Z)-3-{4-[3-(2-Chloro-phenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester (example 3) (400mg, 0.86mmol) was hydrolyzed in an identical manner to example 2 to give the title compound (353mg).

^1H NMR (CDCl_3 , 300 MHz); δ 1.09-1.20 (3H, CH_3), 2.85-3.10 (2H, CH_2), 3.30-3.42 and 3.51-3.65 (2H, OCH_2), 3.96-4.05 (1H, CHCO_2), 4.35-4.50 and 4.70-4.74 (2H, OCH_2) 6.00-6.05 and 6.42-6.49 (1H, CHalkene), 6.71-6.82 (2H, aryl), 7.05-7.50 (remaining H, aryl).

5 MS calcd for $\text{C}_{26}\text{H}_{25}\text{ClO}_4$ 436.9, Found 436.2.

Example 5

3-{4-[3,3-Bis-(4-methoxy-phenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester

10

Reaction of 3, 3-bis(4-methoxy-phenyl)-prop-2-en-1-ol (216mg, 0.8mmol), triphenyl-phosphine (240mg, 0.9mmol), 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (240mg, 1.0 mmol) and diethylazodicarboxylate (0.11mL, 0.9mmol) in an identical manner to Example 1 gave the title compound (90mg).

15

^1H NMR (CDCl_3 , 300 MHz); δ 1.10-1.30 (6H, $2\times\text{CH}_3$), 2.90-2.95 (2H, CH_2), 3.29-3.39 and 3.52-3.65 (2H, OCH_2), 3.78 (3H, OCH_3), 3.82 (3H, OCH_3), 3.90-3.99 (1H, CHCO_2), 4.10-4.20 (2H, OCH_2), 4.51-4.59 (1H, OCH_2) 6.12-6.19 (1H, CHalkene), 6.70-7.45 (remaining H, aryl).

20

MS calcd for $\text{C}_{30}\text{H}_{34}\text{O}_6$ 490.6, Found 488.3.

Example 6

3-{4-[3,3-Bis-(4-methoxy-phenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid

25

3-{4-[3,3-Bis-(4-methoxy-phenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester (example 5) (80mg, 0.16mmol) was hydrolyzed in an identical manner to example 2 to give the title compound (29mg).

30

^1H NMR (CDCl_3 , 300 MHz); δ 1.12-1.20 (3H, CH_3), 2.87-3.09 (2H, CH_2), 3.32-3.49 and 3.52-3.63 (2H, OCH_2), 3.78 (3H, OCH_3), 3.82 (3H, OCH_3), 3.99-4.02 (1H, CHCO_2), 4.51-4.55 (1H, OCH_2) 6.12-6.19 (1H, CHalkene), 6.72-7.23 (remaining H, aryl).

MS calcd for $\text{C}_{28}\text{H}_{30}\text{O}_6$ 462.5, Found 462.1

Example 7(E, Z)-3-{4-[3-phenyl-3-(Biphenyl-4-yl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester

5 Reaction of of 3-phenyl-3-(biphenyl-4-yl)-prop-2-en-1-ol (250mg, 0.66mmol), triphenyl-phosphine (195mg, 0.73mmol), 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (190mg, 0.79 mmol) and diethylazodicarboxylate (0.11mL, 0.79mmol) in an identical manner to Example 1 gave the title compound (180mg).

10 ¹H NMR (CDCl₃, 300 MHz); δ 1.10-1.32 (6H, 2xCH₃), 2.89-2.95 (2H, CH₂), 3.28-3.39 and 3.52-3.63 (2H, OCH₂), 3.91-3.96 (1H, CHCO₂), 4.08-4.20 (2H, OCH₂), 4.51-4.62 (1H, OCH₂) 6.29-6.41 and 6.61-6.70 (1H, CHalkene), 6.72-7.80 (2H, aryl), 7.08-7.18 (2H, aryl), 7.20-7.70 (remaining H, aryl).

MS calcd for C₃₄H₃₄O₄ 506.6, Found 504.2.

15

Example 8(E, Z)-3-{4-[3-phenyl-3-(Biphenyl-4-yl)-allyloxy]-phenyl}-2-ethoxy-propionic acid

20 (E, Z)-3-{4-[3-phenyl-3-(Biphenyl-4-yl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester (example 7) (70mg, 0.13mmol) was hydrolyzed in an identical manner to example 2 to give the title compound (25mg).

¹H NMR (CDCl₃, 300 MHz); δ 1.02-1.23 (3H, CH₃), 2.83-3.12 (2H, CH₂), 3.32-3.50 and 3.52-3.63 (2H, OCH₂), 3.96-4.07 (1H, CHCO₂), 4.51-4.70 (1H, OCH₂) 6.39-6.41 (1H, CHalkene), 6.72-7.82 (2H, aryl), 7.01-7.65 (remaining H, aryl).

25

MS calcd for C₃₂H₃₀O₄ 478.6, Found 478.2

Example 9

30

(E, Z)-2-Ethoxy-3-{4-[3-phenyl-3-(thiophen-2-yl)-allyloxy]-phenyl}-propionic acid ethyl ester

Reaction of 3-phenyl-3-(thiophen-2-yl)-prop-2-en-1-ol (320mg, 1.5mmol), tributylphosphine (0.4mL, 1.6mmol), 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (380mg,

1.6mmol) and azodicarboxylic dipiperidide(403mg, 1.6mmol) in an identical manner to Example 3 gave the title compound (290mg).

¹H NMR (CDCl₃, 300 MHz); δ 1.08-1.32 (6H, 2xCH₃), 2.90-2.99 (2H, CH₂), 3.28-3.39 and 3.52-3.63 (2H, OCH₂), 3.91-3.99 (1H, CHCO₂), 4.08-4.21 (2H, OCH₂), 4.42-4.50 and 4.72-4.80 (1H, OCH₂), 6.19-6.25 and 6.32-6.39 (1H, CHalkene), 6.62-7.48 (remaining H, aryl). MS calcd for C₂₆H₂₈O₄S 436.6, Found 436.1.

Example 10

10

(E, Z)-2-Ethoxy-3-{4-[3-phenyl-3-(thiophen-2-yl)-allyloxy]-phenyl}-propionic acid

15

(E, Z)-2-Ethoxy-3-{4-[3-phenyl-3-(thiophen-2-yl)-allyloxy]-phenyl}-propionic acid ethyl ester (example 9) (200mg, 0.45mmol) was hydrolyzed in an identical manner to example 2 to give the title compound (94mg).

20

¹H NMR (CDCl₃, 300 MHz); δ 1.12-1.31 (3H, CH₃), 2.88-3.10 (2H, CH₂), 3.28-3.48 and 3.52-3.58 (2H, OCH₂), 3.96-4.03 (1H, CHCO₂), 4.42-4.48 and 4.76-4.80 (1H, OCH₂), 6.19-6.22 and 6.32-6.39 (1H, CHalkene), 6.65-7.48 (remaining H, aryl). MS calcd for C₂₄H₂₄O₄S 408.5, Found 408.2.

Example 11

25

2-Ethoxy-3-{4-[3-phenyl-3-(pyridin-2-yl)-allyloxy]-phenyl}-propionic acid ethyl ester

30

Reaction of 3-phenyl-3-(pyridin-2-yl)-prop-2-en-1-ol (320mg, 1.5mmol), tributylphosphine (0.42mL, 1.6mmol), 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (380mg, 1.6mmol) and azodicarboxylic dipiperidide(403mg, 1.6mmol) in an identical manner to Example 3 gave the title compound (650mg).

¹H NMR (CDCl₃, 300 MHz); δ 1.10-1.30 (6H, 2xCH₃), 2.90-2.95 (2H, CH₂), 3.28-3.39 and 3.51-3.62 (2H, OCH₂), 3.90-3.95 (1H, CHCO₂), 4.05-4.20 (2H, OCH₂), 4.53-4.59 (1H, OCH₂), 6.72-6.78 (1H, CHalkene), 6.95-7.60 (remaining H, aryl and pyridyl), 8.58-8.61 (1H, pyridyl).

MS calcd for $C_{27}H_{29}O_4N$ 431.5, Found 431.3.

Example 12

5 2-Ethoxy-3-{4-[3-phenyl-3-(pyridin-2-yl)-allyloxy]-phenyl}-propionic acid

2-Ethoxy-3-{4-[3-phenyl-3-(pyridin-2-yl)-allyloxy]-phenyl}-propionic acid ethyl ester (example 11) (210mg, 0.48mmol) was hydrolyzed in an identical manner to example 2 to give the title compound (110mg).

10

1H NMR ($CDCl_3$, 300 MHz); δ 1.10-1.18 (3H, CH_3), 2.82-3.04 (2H, CH_2), 3.28-3.39 and 3.51-3.62 (2H, OCH_2), 3.92-3.97 (1H, $CHCO_2$), 4.53-4.65 (1H, OCH_2) 6.70-6.78 (1H, CH_{alkene}), 6.88-7.62 (remaining H, aryl and pyridyl), 8.58-8.62 (1H, pyridyl).

MS calcd for $C_{25}H_{25}O_4N$ 403.5, Found 403.2.

15

Example 13

3-[4-(3, 3-Diphenyl-propoxy)-phenyl]-2-ethoxy-propionic acid ethyl ester

20 Reaction of 3, 3-diphenyl-propan-1-ol (110mg, 0.5mmol), triphenylphosphine (145mg, 0.55mmol), 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (140mg, 0.6 mmol) and diethylazodicarboxylate (0.09mL, 0.55mmol) in an identical manner to Example 1 gave the title compound (120mg).

25 1H NMR ($CDCl_3$, 300 MHz); δ 1.10-1.29 (6H, $2 \times CH_3$), 2.44-2.55 (2H, CH_2), 2.90-2.95 (2H, CH_2), 3.28-3.39 and 3.51-3.62 (2H, OCH_2), 3.80-3.89 (2H, CH_2), 3.90-3.95 (1H, $CHCO_2$), 4.10-4.28 (3H, arylCH and OCH_2), 6.70-6.77 (2H, aryl), 7.05-7.35 (remaining H, aryl).

MS calcd for $C_{28}H_{32}O_4$ 432.6, Found 432.3.

30

Example 14

3-[4-(3,3-Diphenyl-propoxy)-phenyl]-2-ethoxy-propionic acid

3-[4-(3, 3-Diphenyl-propoxy)-phenyl]-2-ethoxy-propionic acid ethyl ester (example 13) (110mg, 0.25mmol) was hydrolyzed in an identical manner to example 2 to give the title compound (55mg).

- 5 ¹H NMR (CDCl₃, 300 MHz); δ 1.10-1.19 (3H, CH₃), 2.42-2.55 (2H, CH₂), 2.87-3.08 (2H, CH₂), 3.30-3.47 and 3.51-3.62 (2H, OCH₂), 3.80-3.89 (2H, CH₂), 3.98-4.03 (1H, CHCO₂), 4.10-4.25 (1H, arylCH), 6.70-6.77 (2H, aryl), 7.05-7.35 (remaining H, aryl).
MS calcd for C₂₆H₂₈O₄ 404.5, Found 404.3.

10

Example 152-Ethoxy-3-{4-[3-phenyl-3-(4-methylphenyl)-propoxy]-phenyl}-propionic acid ethyl ester

- 15 Reaction of 3-phenyl-3-(4-methylphenyl)-2-propanol (210mg, 0.88mmol), tributylphosphine (0.25mL, 1.0mmol), 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (240mg, 1.0mmol) and azodicarboxylic dipiperidine (250mg, 1.0mmol) in an identical manner to Example 3 gave the title compound (160mg).

- 20 ¹H NMR (CDCl₃, 300 MHz); δ 1.07-1.28 (6H, 2xCH₃), 2.29 (3H, CH₃), 2.42-2.49 (2H, CH₂), 2.89-2.93 (2H, CH₂), 3.25-3.40 and 3.51-3.61 (2H, OCH₂), 3.88-3.85 (2H, CH₂), 3.90-4.00 (1H, CHCO₂), 4.10-4.19 (3H, arylCH and OCH₂), 6.69-6.73 (2H, aryl), 7.03-7.29 (remaining H, aryl).
MS calcd for C₂₉H₃₄O₄ 446.6, Found 446.3.

25

Example 162-Ethoxy-3-{4-[3-phenyl-3-(4-methylphenyl)-propoxy]-phenyl}-propionic acid

- 30 2-Ethoxy-3-{4-[3-phenyl-3-(4-methylphenyl)-propoxy]-phenyl}-propionic acid ethyl ester (example 15) (130mg, 0.30mmol) was hydrolyzed in an identical manner to example 2 to give the title compound (55mg).

^1H NMR (CDCl_3 , 300 MHz); δ 1.11-1.21 (3H, CH_3), 2.29 (3H, CH_3), 2.42-2.53 (2H, CH_2), 2.83-3.12 (2H, CH_2), 3.38-3.50 and 3.51-3.63 (2H, OCH_2), 3.80-3.88 (2H, CH_2), 3.99-4.05 (1H, CHCO_2), 4.12-4.22 (1H, arylCH), 6.69-6.73 (2H, aryl), 7.03-7.29 (remaining H, aryl).
MS calcd for $\text{C}_{27}\text{H}_{30}\text{O}_4$ 418.5, Found 418.3.

5

Example 173-{4-[3-phenyl-3-(biphenyl-4-yl)-propoxy]-phenyl}-2-ethoxy-propionic acid ethyl ester

10 Reaction of 3-biphenyl-4-yl-3-phenyl-propan-1-ol (145mg, 0.5mmol), triphenylphosphine (145mg, 0.55mmol), 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (140mg, 0.6 mmol) and diethylazodicarboxylate (0.09mL, 0.55mmol) in an identical manner to Example 1 gave the title compound (230mg).

15 ^1H NMR (CDCl_3 , 300 MHz); δ 1.07-1.28 (6H, $2\times\text{CH}_3$), 2.48-2.55 (2H, CH_2), 2.89-2.93 (2H, CH_2), 3.25-3.40 and 3.51-3.63 (2H, OCH_2), 3.88-4.00 (3H, CH_2 and CHCO_2), 4.10-4.19 (2H, OCH_2), 4.20-4.30 (1H, CH), 6.67-6.71 (2H, aryl), 7.05-7.55 (remaining H, aryl).
MS calcd for $\text{C}_{34}\text{H}_{36}\text{O}_4$ 508.7, Found 508.3.

20

Example 183-{4-[3-phenyl-3-(biphenyl-4-yl)-propoxy]-phenyl}-2-ethoxy-propionic acid

25 3-{4-[3-phenyl-3-(biphenyl-4-yl)-propoxy]-phenyl}-2-ethoxy-propionic acid ethyl ester (example 17) (200mg, 0.39mmol) was hydrolyzed in an identical manner to example 2 to give the title compound (70mg).

30 ^1H NMR (CDCl_3 , 300 MHz); δ 1.07-1.20 (3H, CH_3), 2.49-2.61 (2H, CH_2), 2.88-3.09 (2H, CH_2), 3.32-3.48 and 3.51-3.66 (2H, OCH_2), 3.88-3.92 (2H, CH_2) 3.95-4.05 (1H, CHCO_2), 4.20-4.30 (1H, CH), 6.67-6.79 (2H, aryl), 7.05-7.55 (remaining H, aryl).
MS calcd for $\text{C}_{32}\text{H}_{32}\text{O}_4$ 480.6, Found 480.3.

Example 19

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2-{4-[3,3-Bis-(4-methoxy-phenyl)-allyloxy]-benzyl}-malonic acid dimethyl ester

Under a nitrogen atmosphere, 3,3-bis-(4-methoxy-phenyl)-prop-2-en-1-ol (500 mg, 1.95 mmol), tributylphosphine (424 mg, 2.1 mmol) and 2-(4-hydroxy-benzyl)-malonic acid dimethyl ester (464 mg, 1.95 mmol) were successively dissolved in dry benzene (50 mL).
 5 Solid azodicarboxylic dipiperidide (ADDP) (530 mg, 2.1 mmol) was added under stirring at 0°C to the solution. After 10 min, the reaction mixture was brought to room temperature and the stirring was continued for 16 h. Heptane (10 mL) was added to the reaction mixture and di hydro-ADDP separated out was filtered off. After evaporation of the solvent the product
 10 was purified by chromatography eluting with heptane/ethylacetate (4:1) to give 150 mg (16%) of the title compound.

¹H NMR (CDCl₃, 300 MHz); δ 3.15 (2H, PhCH₂), 3.63 (1H, CH), 3.70 (6H, 2xCO₂CH₃), 3.80 (3H, PhOCH₃), 3.83 (3H, PhOCH₃), 4.55 (1H, OCH₂), 6.15 (1H, CHalkene), 6.70-7.20 (re-
 15 maining H, aryl).

Example 20

(E)-(2S)-2-Ethoxy-3-{4-[3-(4-furan-2-yl-phenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid ethyl ester
 20 ester

Reaction of (E)-3-(4-furan-2-yl-phenyl)-3-phenyl-prop-2-en-1-ol (475 mg, 1.72 mmol), tributylphosphine (0.63 ml, 2.58 mmol), (2S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (451 mg, 1.89 mmol) and azodicarboxylic dipiperidide (650 mg, 2.58 mmol) in benzene
 25 in an identical manner to example 3 gave the title compound (450 mg, 53%).

¹H NMR (CDCl₃, 300 MHz); δ 1.16 (3H, t), 1.21 (3H, t), 2.93 (2H, d), 3.26-3.40 (1H, m), 3.52-3.64 (1H, m), 3.94 (1H, t), 4.14 (2H, q), 4.58 (2H, d), 6.36 (1H, t), 6.47 (1H, dd), 6.63 (1H, d), 6.77 (2H, dm), 7.12 (2H, dm), 7.16-7.31 (4H, m), 7.31-7.50 (4H, m), 7.58 (2H, dm).
 30

Example 21

(E)-(2S)-2-Ethoxy-3-{4-[3-(4-furan-2-yl-phenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid

(*E*)-(2*S*)-2-Ethoxy-3-{4-[3-(4-furan-2-yl-phenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid ethyl ester (example 20) (440 mg, 0.89 mmol) was hydrolyzed in an identical manner to example 2 to give the title compound (408 mg, 97%)

- 5 ¹H NMR (CDCl₃, 300 MHz); δ 1.17 (3H, t), 2.93 (1H, dd), 3.07 (1H, dd), 3.39-3.52 (1H, m), 3.52-3.64 (1H, m), 4.04 (1H, dd), 4.58 (2H, d), 6.36 (1H, t), 6.48 (1H, m), 6.63 (1H, d), 6.79 (2H, dm), 7.12 (2H, dm), 7.16-7.32 (4H, m), 7.32-7.50 (4H, m), 7.59 (2H, dm), COOH too broad to be observed.
LCMS (electrospray): 491 (M+Na), 259 (100%).

10

Example 22

(*E*)-(2*S*)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester

- 15 Reaction of (*E*)-3-biphenyl-4-yl-3-phenyl-prop-2-en-1-ol (1.0 g, 3.49 mmol), tributylphosphine (1.3 ml, 5.24 mmol), (2*S*)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (0.92 g, 3.84 mmol) and azodicarboxylic dipiperidide (1.32 g, 5.24 mmol) in benzene in an identical manner to example 3 gave the title compound (1.47 g, 83%).
- 20 ¹H NMR (CDCl₃, 300 MHz); δ 1.16 (3H, t), 1.21 (3H, t), 2.95 (2H, d), 3.28-3.40 (1H, m), 3.53-3.65 (1H, m), 3.95 (1H, t), 4.15 (2H, q), 4.57 (2H, d), 6.39 (1H, t), 6.78 (2H, dm), 7.12 (2H, dm), 7.20-7.48 (10H, m), 7.48-7.62 (4H, m).

Example 23

25

(*E*)-(2*S*)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid

- (*E*)-(2*S*)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester (example 22) (1.38 g, 2.72 mmol) was hydrolyzed in an identical manner to example 2 to
30 give the title compound (1.25 mg, 96%)

¹H NMR (CDCl₃, 300 MHz); δ 1.17 (3H, t), 2.95 (1H, dd), 3.06 (1H, dd), 3.37-3.52 (1H, m), 3.52-3.64 (1H, m), 4.03 (1H, dd), 4.59 (2H, d), 6.38 (1H, t), 6.78 (2H, m), 7.12 (2H, dm), 7.20-7.49 (10H, m), 7.49-7.62 (4H, m), COOH too broad to be observed.

Example 24

(E, Z)-(2S)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester

Reaction of (E, Z)-3-biphenyl-4-yl-3-phenyl-prop-2-en-1-ol (601 mg, 2.1 mmol), triphenylphosphine (606 mg, 2.31 mmol), (2S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (601 mg, 2.52 mmol) and diethyl lazodicarboxylate (402 mg, 2.31 mmol) in an identical manner to example 1 gave the title compound (400 mg, 38%).

¹H NMR (CDCl₃, 200 MHz); δ 1.10-1.30 (6H, m), 2.94 (2H, d), 3.25-3.45 (1H, m), 3.50-3.65 (1H, m), 3.96 (1H, t), 4.16 (2H, dd), 4.55-4.68 (2H, d), 6.30-6.44 (1H, m), 6.73-6.84 (2H, m), 7.14 (2H, dm), 7.20-7.70 (14H, m).

Example 25

(E, Z)-(2S)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid

(E, Z)-(2S)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester (example 24) (400 mg, 0.79 mmol) was hydrolyzed in an identical manner to example 2 to give the title compound (250 mg, 66%)

¹H NMR (CDCl₃, 300 MHz); δ 1.05-1.20 (3H, m), 2.94 (1H, dd), 3.01 (1H, dd), 3.30-3.43 (1H, m), 3.50-3.68 (1H, m), 4.00 (1H, dd), 4.50-4.68 (2H, m), 6.27-6.40 (1H, m), 6.72-6.84 (2H, m), 7.12 (2H, dm), 7.18-7.65 (14H, m), 9.85 (1H, br s).

Example 26

3-[4-[3,3-Bis-(3-methyl-thiophen-2-yl)-allyloxy]-phenyl]-2-ethoxy-propionic acid ethyl ester

Reaction of 3,3-bis-(3-methylthiophen-2-yl)-prop-2-en-1-ol (1.0 mg, 3.99 mmol), tributylphosphine (0.91 g, 4.5 mmol), 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (1.07

g, 4.5 mmol) and azodicarboxylic dipiperidide (1.14 g, 4.5 mmol) in an identical manner to example 3 gave the title compound (680 mg, 36%).

¹H NMR (CDCl₃, 200 MHz); δ 1.15 (3H, t), 1.23 (3H, t), 2.00 (3H, s), 2.08 (3H, s), 2.93 (2H, d), 3.28-3.40 (1H, m), 3.50-3.64 (1H, m), 3.94 (1H, t), 4.14 (2H, dd), 4.58 (2H, d), 6.24 (1H, t), 6.70-6.81 (3H, m), 6.88 (1H, d), 7.04-7.15 (3H, m), 7.21-7.30 (1H, m).

Example 27

10 3-{4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester

Reaction of 3,3-bis-(4-bromophenyl)-prop-2-en-1-ol (0.50 g, 1.36 mmol), triphenylphosphine (0.39 g, 1.50 mmol), 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (0.39 g, 1.63 mmol) and diethyl azodicarboxylate (0.26 g, 1.51 mmol) in an identical manner to example 1 gave the title compound (450 mg, 56%).

¹H NMR (CDCl₃, 300 MHz); δ 1.15 (3H, t), 1.22 (3H, t), 2.94 (2H, d), 3.28-3.42 (1H, m), 3.53-3.65 (1H, m), 3.96 (1H, t), 4.16 (2H, q), 4.52 (2H, d), 6.32 (1H, t), 6.75 (2H, dm), 7.01-7.20 (6H, m), 7.43 (2H, dm), 7.52 (2H, dm).
20 MS (EI): 586/588/590 (M⁺), 513/515/517, 349/351/353 (100%).

Example 28

25 3-{4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid

3-{4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester (example 27) (150 mg, 0.25 mmol) was hydrolyzed in an identical manner to example 2 to give the title compound (135 mg, 96%)

30 ¹H NMR (CDCl₃, 300 MHz); δ 1.17 (3H, t), 2.94 (1H, dd), 3.06 (1H, dd), 3.40-3.52 (1H, m), 3.52-3.66 (1H, m), 4.04 (1H, dd), 4.51 (2H, d), 6.30 (1H, t), 6.76 (2H, dm), 7.00-7.20 (6H, m), 7.42 (2H, dm), 7.52 (2H, dm), COOH too broad to be observed.
MS (EI): 558/560/562 (M⁺), 349/351/353, 270/272 (100%), 191.

Example 292-Ethoxy-3-[4-(3-phenyl-3-pyridin-4-yl-allyloxy)-phenyl]-propionic acid ethyl ester

5 Reaction of 3-phenyl-3-pyridin-4-yl-prop-2-en-1-ol (0.50 g, 2.37 mmol), triphenylphosphine (0.68 g, 2.61 mmol), 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (0.68 g, 2.84 mmol) and diethyl azodicarboxylate (0.46 g, 2.63 mmol) in an identical manner to example 1 gave the title compound (435 mg, 43%).

10 ¹H NMR (CDCl₃, 200 MHz); δ 1.16 (3H, t), 1.21 (3H, t), 2.94 (2H, d), 3.25-3.43 (1H, m), 3.50-3.70 (1H, m), 3.98 (1H, t), 4.17 (2H, q), 4.52 (2H, d), 6.41 (1H, t), 6.76 (2H, dm), 7.05-7.40 (9H, m), 8.66 (2H, dm).

MS (EI): 431 (M⁺), 194 (100%).

Mp. 84-87°C

15

Example 302-Ethoxy-3-[4-(3-phenyl-3-pyridin-4-yl-allyloxy)-phenyl]-propionic acid

20 2-Ethoxy-3-[4-(3-phenyl-3-pyridin-4-yl-allyloxy)-phenyl]-propionic acid ethyl ester (example 29) (200 mg, 0.46 mmol) was hydrolyzed in an identical manner to example 2 to give the title compound (50 mg, 27%)

¹H NMR (CDCl₃, 300 MHz); δ 1.16 (3H, t), 2.98 (1H, dd), 3.06 (1H, dd), 3.33-3.49 (1H, m),
25 3.60-3.75 (1H, m), 4.03 (1H, dd), 4.52 (2H, d), 6.46 (1H, t), 6.78 (2H, dm), 7.09-7.40 (9H, m), 8.63 (2H, dm), 9.23 (1H, br s).

Example 31

30 (E, Z)-(2S)-2-Ethoxy-3-[4-[3-(4-methoxyphenyl)-3-thiophen-2-yl-allyloxy]-phenyl]-propionic acid ethyl ester

Reaction of 3-(4-methoxyphenyl)-3-thiophen-2-yl-prop-2-en-1-ol (271 mg, 1.10 mmol), triphenylphosphine (289 mg, 1.10 mmol), (2S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid

ethyl ester (238 mg, 1.0 mmol) and diethyl azodicarboxylate (188 mg, 1.08 mmol) in an identical manner to example 1 gave the title compound (80 mg, 17%).

¹H NMR (CDCl₃, 200 MHz); δ 1.10-1.28 (6H, m), 2.88-2.98 (2H, m), 3.25-3.43 (1H, m), 3.47-3.69 (1H, m), 3.77-3.90 (3H, m), 3.95 (1H, tm), 4.16 (2H, q), 4.45-4.78 (2H, m), 6.10-6.48 (1H, m), 6.70-7.50 (11H, m).

Example 32

10 (E, Z)-(2S)-2-Ethoxy-3-[4-[3-(4-methoxyphenyl)-3-thiophen-2-yl-allyloxy]-phenyl]-propionic acid

(E, Z)-(2S)-2-Ethoxy-3-[4-[3-(4-methoxyphenyl)-3-thiophen-2-yl-allyloxy]-phenyl]-propionic acid ethyl ester (example 31) (75 mg, 0.16 mmol) was hydrolyzed in an identical manner to example 2 to give the title compound (40 mg, 57%)

¹H NMR (CDCl₃, 300 MHz); δ 1.17 (3H, t), 2.83-3.13 (2H, m), 3.27-3.50 (1H, m), 3.50-3.70 (1H, m), 3.77-3.88 (3H, m), 3.97-4.09 (1H, m), 4.43-4.28 (2H, m), 6.10-6.30 (1H, m), 6.70-7.40 (11H, m), COOH too broad to be observed.

20 MS (EI): 438 (M⁺), 229 (100%).

Example 33

25 (E, Z)-(2S)-2-Ethoxy-3-[4-(3-phenyl-3-p-tolyl-allyloxy)-phenyl]-propionic acid ethyl ester

Reaction of (E, Z)-3-phenyl-3-tolyl-prop-2-en-1-ol (841 mg, 3.75 mmol), triphenylphosphine (1.03 g, 3.93 mmol), (2S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (851 mg, 3.57 mmol) and diethyl azodicarboxylate (656 mg, 3.94 mmol) in an identical manner to example 1 gave the title compound (0.64 g, 40%).

30 ¹H NMR (CDCl₃, 300 MHz); δ 1.14 (3H, t), 1.22 (3H, t), 2.30-2.42 (3H, m), 2.93 (2H, d), 3.26-3.40 (1H, m), 3.51-3.66 (1H, m), 3.94 (1H, t), 4.16 (2H, q), 4.49-4.63 (2H, m), 6.20-6.33 (1H, m), 6.76 (2H, dm), 7.00-7.45 (11H, m).

MS (EI): 444 (M⁺), 207 (100%).

Example 34(E, Z)-(2S)-2-Ethoxy-3-[4-(3-phenyl-3-p-tolyl-allyloxy)-phenyl]-propionic acid

5

(E, Z)-(2S)-2-Ethoxy-3-[4-(3-phenyl-3-p-tolyl-allyloxy)-phenyl]-propionic acid ethyl ester (example 33) (0.55 g, 1.24 mmol) was hydrolyzed in an identical manner to example 2 to give the title compound (0.50 g, 97%)

10 ¹H NMR (CDCl₃, 300 MHz); δ 1.17 (3H, t), 2.24-2.41 (3H, m), 2.93 (1H, dd), 3.04 (1H, dd), 3.37-3.64 (2H, m), 4.03 (1H, dd), 4.50-4.63 (2H, m), 6.20-6.32 (1H, m), 6.78 (2H, dm), 7.00-7.43 (11H, m), COOH too broad to be observed.
MS (EI): 416 (M⁺), 207 (100%).

15

Example 35(2S)-3-[4-(3,3-Diphenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester

20 Reaction of 3,3-diphenyl-prop-2-en-1-ol (210 mg, 1.0 mmol), tributylphosphine (303 mg, 1.50 mmol), (2S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (250 mg, 1.05 mmol) and azodicarboxylic dipiperidide (378 mg, 1.50 mmol) in an identical manner to example 3 gave the title compound (290 mg, 67%).

25 ¹H NMR (CDCl₃, 300 MHz); δ 1.14 (3H, t), 1.21 (3H, t), 2.92 (2H, d), 3.28-3.40 (1H, m), 3.52-3.65 (1H, m), 3.94 (1H, t), 4.14 (2H, q), 4.56 (2H, d), 6.31 (1H, t), 6.75 (2H, dm), 7.10 (2H, dm), 7.16-7.44 (10H, m).

Example 3630 (2S)-3-[4-(3,3-Diphenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid

(2S)-3-[4-(3,3-Diphenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester (example 35) (215 mg, 0.50 mmol) was hydrolyzed in an identical manner to example 2 to give the title compound (180 mg, 90%)

(E)-(2S)-2-Ethoxy-3-{4-[3-(4-fluorophenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid ethyl ester

5 Reaction of (*E*)-3-(4-fluorophenyl)-3-phenyl-prop-2-en-1-ol (200 mg, 0.88 mmol), triphenylphosphine (242 mg, 0.92 mmol), (*2S*)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (200 mg, 0.84 mmol) and diethyl azodicarboxylate (160 mg, 0.92 mmol) in an identical manner to example 1 gave the title compound (320 mg, 85%).

10 ¹H NMR (CDCl₃, 300 MHz); δ 1.15 (3H, t), 1.21 (3H, t), 2.93 (2H, d), 3.24-3.43 (1H, m), 3.50-3.67 (1H, m), 3.96 (1H, t), 4.16 (2H, q), 4.54 (2H, d), 6.25 (1H, t), 6.75 (2H, dm), 6.90-7.03 (2H, m), 7.03-7.30 (6H, m), 7.30-7.45 (3H, m).
MS (EI): 448 (M⁺), 375, 211 (100%).

15 Example 40

(E)-(2S)-2-Ethoxy-3-{4-[3-(4-fluorophenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid

(*E*)-(2*S*)-2-Ethoxy-3-{4-[3-(4-fluorophenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid ethyl ester (example 39) (225 mg, 0.50 mmol) was hydrolyzed in an identical manner to example 2 to give the title compound (245 mg, 95%)

¹H NMR (CDCl₃, 200 MHz); δ 1.17 (3H, t), 2.83-3.14 (2H, m), 3.34-3.68 (2H, m), 4.02 (1H, dd), 4.53 (2H, d), 6.24 (1H, t), 6.78 (2H, dm), 6.89-7.05 (2H, m), 7.05-7.49 (9H, m), COOH too broad to be observed.

MS (EI): 420 (M⁺), 317, 211 (100%).

Example 41

30 (2S)-3-{4-[3,3-Bis-(4-methoxyphenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester

Reaction of 3,3-bis-(4-methoxyphenyl)-prop-2-en-1-ol (1.62 g, 5.99 mmol), triphenylphosphine (2.88 g, 10.98 mmol), (2S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl

ester (1.19 g, 4.99 mmol) and diethyl lazodicarboxylate (1.92 g, 11.04 mmol) in an identical manner to example 1 gave the title compound (0.434 g, 17%).

¹H NMR (CDCl₃, 300 MHz); δ 1.15 (3H, t), 1.21 (3H, t), 2.93 (2H, d), 3.27-3.41 (1H, m), 3.53-3.65 (1H, m), 3.80 (3H, s), 3.84 (3H, s), 3.95 (1H, t), 4.15 (2H, q), 4.56 (2H, d), 6.17 (1H, t), 6.71-6.87 (4H, m), 6.92 (2H, dm), 7.05-7.25 (6H, m).

Example 42

10 (2S)-3-[4-[3,3-Bis-(4-methoxyphenyl)-allyloxy]-phenyl]-2-ethoxy-propionic acid

(2S)-3-[4-[3,3-Bis-(4-methoxyphenyl)-allyloxy]-phenyl]-2-ethoxy-propionic acid ethyl ester (example 41) (225 mg, 0.495 mmol) was hydrolyzed in an identical manner to example 2 to give the title compound (150 mg, 71%)

15 ¹H NMR (CDCl₃, 300 MHz); δ 1.17 (3H, t), 2.95 (1H, dd), 3.04 (1H, dd), 3.38-3.50 (1H, m), 3.52-3.66 (1H, m), 3.80 (3H, s), 3.83 (3H, s), 4.03 (1H, dd), 4.57 (2H, d), 6.17 (1H, t), 6.71-6.85 (4H, m), 6.92 (2H, dm), 7.05-7.25 (6H, m), COOH too broad to be observed.

20 Example 43

(2S)-3-[4-(3,3-Di-p-tolyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester

Reaction of 3,3-di-(4-methylphenyl)-prop-2-en-1-ol (1.0 g, 4.20 mmol), tributylphosphine (1.27 g, 6.30 mmol), (2S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (1.10 g, 4.62 mmol) and azodicarboxylic dipiperidide (1.59 g, 6.30 mmol) in an identical manner to example 3 gave the title compound (0.76 g, 39%).

25 ¹H NMR (CDCl₃, 300 MHz); δ 1.13 (3H, t), 1.21 (3H, t), 2.33 (3H, s), 2.38 (3H, s), 2.93 (2H, d), 3.26-3.41 (1H, m), 3.52-3.66 (1H, m), 3.95 (1H, t), 4.15 (2H, q), 4.56 (2H, d), 6.27 (1H, t), 6.75 (2H, dm), 7.00-7.21 (10H, m).

30 MS (EI): 458 (M⁺), 385, 221 (100%).

Example 44(2S)-3-[4-(3,3-Di-p-tolyl-allyloxy)-phenyl]-2-ethoxy-propionic acid

5 (2S)-3-[4-(3,3-Di-p-tolyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester (example 43) (0.76 g, 1.66 mmol) was hydrolyzed in an identical manner to example 2 to give the title compound (0.696 g, 98%).

¹H NMR (CDCl₃, 300 MHz); δ 1.16 (3H, t), 2.33 (3H, s), 2.38 (3H, s), 2.94 (1H, dd), 3.05 (1H, dd), 3.39-3.51 (1H, m), 3.51-3.65 (1H, m), 4.03 (1H, dd), 4.57 (2H, d), 6.23 (1H, t), 6.77 (2H, dm), 7.00-7.22 (10H, m), COOH too broad to be observed.
10 MS (EI): 430 (M⁺), 327, 221 (100%).

Example 45

15 (Z)-(2S)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester

Reaction of (Z)-3-biphenyl-4-yl-3-phenyl-prop-2-en-1-ol (171 mg, 0.60 mmol), triphenyl-phosphine (142 mg, 0.63 mmol), (2S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (149 mg, 0.63 mmol) and diethyl azodicarboxylate (95 mg, 0.55 mmol) in an identical
20 manner to example 1 gave the title compound (160 mg, 53%).

¹H NMR (CDCl₃, 300 MHz); δ 1.16 (3H, t), 1.21 (3H, t), 2.93 (2H, d), 3.28-3.40 (1H, m), 3.52-3.65 (1H, m), 3.95 (1H, t), 4.14 (2H, q), 4.63 (2H, d), 6.33 (1H, t), 6.78 (2H, dm), 7.12 (2H, dm), 7.20-7.50 (10H, m), 7.55-7.68 (4H, m).
25

Example 46

(Z)-(2S)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid

30 (Z)-(2S)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester (example 45) (0.36 g, 0.71 mmol) was hydrolyzed in an identical manner to example 2 to give the title compound (0.345 g, 86%) as an orange gum containing approximately 0.6 molar equivalents of ethyl acetate.

¹H NMR (CDCl₃, 300 MHz); δ 1.17 (3H, t), 1.26 (1.8H, t, ethyl acetate), 2.04 (1.8H, s, ethyl acetate), 2.95 (1H, dd), 3.06 (1H, dd), 3.38-3.52 (1H, m), 3.52-3.64 (1H, m), 4.03 (1H, dd), 4.12 (1.2H, q, ethyl acetate), 4.63 (2H, d), 6.32 (1H, t), 6.80 (2H, dm), 7.11 (2H, dm), 7.20-7.50 (10H, m), 7.54-7.68 (4H, m), COOH too broad to be observed.
MS (EI): 478 (M⁺), 375, 269 (100%).

Example 47

10 (Z)-(2S)-3-{4-[3-(4-Bromophenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester

Reaction of 3-(4-bromophenyl)-3-phenyl-prop-2-en-1-ol (145 mg, 0.50 mmol), triphenylphosphine (144 mg, 0.55 mmol), (2S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (119 mg, 0.50 mmol) and diethyl azodicarboxylate (96 mg, 0.55 mmol) in an identical manner to example 1 gave the title compound (110 mg, 43%).

¹H NMR (CDCl₃, 300 MHz); δ 1.17 (3H, t), 1.21 (3H, t), 2.94 (2H, d), 3.29-3.41 (1H, m), 3.53-3.65 (1H, m), 3.96 (1H, t), 4.15 (2H, q), 4.53 (2H, d), 6.32 (1H, t), 6.75 (2H, dm), 7.05-7.18 (4H, m), 7.18-7.38 (5H, m), 7.52 (2H, dm).

MS (EI): 508/510 (M⁺) 435/437, 393/395, 271/273, 192 (100%).

Microanalysis for C₂₈H₂₉BrO₄ + 0.1 H₂O: calculated = 65.78%C, 5.76%H; found 65.79%C, 5.91%H.

25

Example 48

(Z)-(2S)-3-{4-[3-(4-Bromophenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid

(Z)-(2S)-3-{4-[3-(4-Bromophenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester (example 47) (90 mg, 0.18 mmol) was hydrolyzed in an identical manner to example 2 to give the title compound (60 mg, 71%).

30

¹H NMR (CDCl₃, 300 MHz); δ 1.17 (3H, t), 2.96 (1H, dd), 3.05 (1H, dd), 3.39-3.51 (1H, m), 3.51-3.64 (1H, m), 4.03 (1H, dd), 4.52 (2H, d), 6.32 (1H, t), 6.75 (2H, dm), 7.02-7.18 (4H, m), 7.18-7.40 (5H, m), 7.51 (2H, dm), COOH too broad to be observed.

LCMS (electrospray): 503/505 (M+Na), 498/500 (M+NH₄), 271/273 (100%).

5

Example 49

(2S)-3-[4-(3,3-Bis-biphenyl-4-yl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester

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Reaction of 3,3-bis-biphenyl-4-yl-prop-2-en-1-ol (363 mg, 1.0 mmol), tributylphosphine (303 mg, 1.5 mmol), (2S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (262 mg, 1.1 mmol) and azodicarboxylic dipiperidide (378 mg, 1.5 mmol) in an identical manner to example 3 gave the title compound (445 mg, 76%) containing 0.8 equivalents of ethyl acetate.

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¹H NMR (CDCl₃, 300 MHz); δ 1.16 (3H, t), 1.21 (3H, t), 1.25 (2.4H, t, ethyl acetate), 2.04 (2.4H, s, ethyl acetate), 2.93 (2H, d), 3.28-3.40 (1H, m), 3.51-3.65 (1H, m), 3.96 (1H, t), 4.07-4.20 (2H, q) plus {1.6H, q, ethyl acetate}, 4.54 (2H, d), 6.40 (1H, t), 6.80 (2H, dm), 7.03 (2H, dm), 7.27-7.70 (18H, m).

20

Example 50

(2S)-3-[4-(3,3-Bis-biphenyl-4-yl-allyloxy)-phenyl]-2-ethoxy-propionic acid

(2S)-3-[4-(3,3-Bis-biphenyl-4-yl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester (example 49) (560 mg, 0.96 mmol) was hydrolyzed in an identical manner to example 2 to give the title compound (450 mg, 84%).

¹H NMR (CDCl₃, 300 MHz); δ 1.13 (3H, t), 2.93 (1H, dd), 3.05 (1H, dd), 3.35-3.50 (1H, m), 3.50-3.64 (1H, m), 4.02 (1H, dd), 4.62 (2H, d), 6.39 (1H, t), 6.80 (2H, dm), 7.02 (2H, dm), 7.27-7.72 (18H, m), COOH too broad to be observed.

30

Example 51

003740 " 01273360

(2S)-3-{4-[3,3-Bis-(4-bromophenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester

Reaction of 3,3-bis-(4-bromophenyl)-prop-2-en-1-ol (2.60 g, 7.0 mmol), tributylphosphine (2.52 g, 10.0 mmol), (2S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (1.50 g, 6.3 mmol) and azodicarboxylic dipiperidide (2.02 g, 10.0 mmol) in an identical manner to example 3 gave the title compound (2.8 g, 75%).

¹H NMR (CDCl₃, 300 MHz); δ 1.16 (3H, t), 1.21 (3H, t), 2.93 (2H, d), 3.27-3.40 (1H, m), 3.53-3.65 (1H, m), 3.94 (1H, t), 4.15 (2H, q), 4.51 (2H, d), 6.31 (1H, t), 6.75 (2H, dm), 7.01-7.19 (6H, m), 7.42 (2H, dm), 7.52 (2H, dm).

Example 52

(2S)-3-{4-[3,3-Bis-(4-bromophenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid

(2S)-3-{4-[3,3-Bis-(4-bromophenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester (example 51) (2.8 g, 4.76 mmol) was hydrolyzed in an identical manner to example 2 to give the title compound (2.3 g, 83%) which contained approximately 0.25 molar equivalents of ethyl acetate.

¹H NMR (CDCl₃, 300 MHz); δ 1.15 (3H, t), 1.25 (0.75H, t, ethyl acetate), 2.04 (0.75H, s, ethyl acetate), 2.93 (1H, dd), 3.04 (1H, dd), 3.37-3.49 (1H, m), 3.52-3.68 (1H, m), 4.02 (1H, dd), 4.12 (0.5H, q, ethyl acetate), 4.50 (2H, d), 6.30 (1H, t), 6.74 (2H, dm), 7.00-7.19 (6H, m), 7.49 (2H, dm), 7.50 (2H, dm), COOH too broad to be observed.

Example 53

(Z)-(2S)-2-Ethoxy-3-{4-[3-(4-furan-2-yl-phenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid ethyl ester

Reaction of (Z)-3-(4-furan-2-yl-phenyl)-3-phenyl-prop-2-en-1-ol (300 mg, 1.09 mmol), tributylphosphine (0.40 ml, 1.64 mmol), (2S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (286 mg, 1.20 mmol) and azodicarboxylic dipiperidide (413 mg, 1.64 mmol) in benzene in an identical manner to example 3 gave the title compound (260 mg, 48%).

¹H NMR (CDCl₃, 300 MHz); δ 1.15 (3H, t), 1.21 (3H, t), 2.93 (2H, d), 3.28-3.40 (1H, m), 3.52-3.65 (1H, m), 3.94 (1H, t), 4.14 (2H, q), 4.60 (2H, d), 6.30 (1H, t), 6.49 (1H, dd), 6.69 (1H, d), 6.77 (2H, dm), 7.11 (2H, dm), 7.18-7.32 (7H, m), 7.49 (1H, d), 7.69 (2H, dm).

5 LCMS (electrospray): 519 (M+Na), 514 (M+NH₄), 259 (100%).

Example 54

10

(Z)-(2S)-2-Ethoxy-3-{4-[3-(4-furan-2-yl-phenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid

(Z)-(2S)-2-Ethoxy-3-{4-[3-(4-furan-2-yl-phenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid ethyl ester (example 53) (240 mg, 0.483 mmol) was hydrolyzed in an identical manner to example

15 2 to give the title compound (170 mg, 75%).

¹H NMR (CDCl₃, 300 MHz); δ 1.15 (3H, t), 2.93 (1H, dd), 3.05 (1H, dd), 3.33-3.49 (1H, m), 3.50-3.65 (1H, m), 4.01 (1H, dd), 4.60 (2H, d), 6.30 (1H, t), 6.49 (1H, dd), 6.68 (1H, d), 6.78 (2H, dm), 7.11 (2H, dm), 7.15-7.36 (7H, m), 7.49 (1H, d), 7.68 (2H, dm), COOH too broad to

20 be observed.

LCMS (electrospray): 491 (M+Na), 486 (M+NH₄), 259 (100%).

Example 55

25 (E)-(2S)-3-{4-[3-(4-Bromophenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester

Reaction of (E)- 3-(4-bromophenyl)-3-phenyl-prop-2-en-1-ol (289 mg, 1.0 mmol), tributylphosphine (0.37 ml, 1.5 mmol), (2S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (262 mg, 1.10 mmol) and azodicarboxylic dipiperidide (378 mg, 1.5 mmol) in benzene in

30

an identical manner to example 3 gave the title compound (460 mg, 90%).

¹H NMR (CDCl₃, 300 MHz); δ 1.15 (3H, t), 1.21 (3H, t), 2.92 (2H, d), 3.26-3.40 (1H, m), 3.51-3.65 (1H, m), 3.94 (1H, t), 4.15 (2H, q), 4.54 (2H, d), 6.29 (1H, t), 6.74 (2H, dm), 7.03-7.45 (11H, m).

LCMS (electrospray): 531/533 (M+Na), 271/273 (100%).

5

Example 56

(E)-(2S)-3-{4-[3-(4-Bromophenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid

- 10 (E)-(2S)-3-{4-[3-(4-Bromophenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester (example 55) (382 mg, 0.75 mmol) was hydrolyzed in an identical manner to example 2 to give the title compound (350 mg, 97%).

- ¹H NMR (CDCl₃, 300 MHz); δ 1.16 (3H, t), 2.93 (1H, dd), 3.05 (1H, dd), 3.38-3.50 (1H, m),
15 3.50-3.63 (1H, m), 4.03 (1H, dd), 4.53 (2H, d), 6.30 (1H, t), 6.75 (2H, dm), 7.03-7.45 (11H, m), COOH too broad to be observed.

LCMS (electrospray): 503/505 (M+Na), 498/500 (M+NH₄), 271/273 (100%).

Example 57

20

(2S)-3-{4-[3,3-Bis-(4-furan-2-yl-phenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester

- Reaction of 3,3-bis-(4-furan-2-yl-phenyl)-prop-2-en-1-ol (460 mg, 1.34 mmol), tributylphosphine (0.50 ml, 2.0 mmol), (2S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester
25 (320 mg, 1.34 mmol) and azodicarboxylic dipiperidide (504 mg, 2.0 mmol) in benzene in an identical manner to example 3 gave the title compound (541 mg, 72%).

- ¹H NMR (CDCl₃, 300 MHz); δ 1.16 (3H, t), 1.21 (3H, t), 2.93 (2H, d), 3.28-3.40 (1H, m), 3.51-3.64 (1H, m), 3.94 (1H, t), 4.14 (2H, q), 4.59 (2H, d), 6.35 (1H, t), 6.40-6.51 (2H, m), 6.62
30 (1H, d), 6.69 (1H, d), 6.77 (2H, dm), 7.13 (2H, dm), 7.20-7.33 (4H, m), 7.44 (1H, d), 7.48 (1H, d), 7.58 (2H, dm), 7.70 (2H, m).

Example 58

(2S)-3-[4-[3,3-Bis-(4-furan-2-yl-phenyl)-allyloxy]-phenyl]-2-ethoxy-propionic acid

(2S)-3-[4-[3,3-Bis-(4-furan-2-yl-phenyl)-allyloxy]-phenyl]-2-ethoxy-propionic acid ethyl ester (example 57) (530 mg, 0.95 mmol) was hydrolyzed in an identical manner to example 2 to give the title compound (400 mg, 79%).

¹H NMR (CDCl₃, 300 MHz); δ 1.17 (3H, t), 2.95 (1H, dd), 3.07 (1H, dd), 3.40-3.52 (1H, m), 3.52-3.63 (1H, m), 4.05 (1H, dd), 4.60 (2H, d), 6.35 (1H, t), 6.44-6.51 (2H, m), 6.64 (1H, d), 6.70 (1H, d), 6.79 (2H, dm), 7.12 (2H, dm), 7.20-7.34 (4H, m), 7.47 (1H, d), 7.50 (1H, d), 7.59 (2H, dm), 7.70 (2H, dm), COOH too broad to be observed.

Example 59

(E, Z)-(2S)-3-[4-(3-Biphenyl-4-yl-3-p-tolyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester

Reaction of (E, Z)-3-biphenyl-4-yl-3-p-tolyl-prop-2-en-1-ol (300 mg, 1.0 mmol), tributylphosphine (0.37 ml, 1.5 mmol), (2S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (262 mg, 1.10 mmol) and azodicarboxylic dipiperidide (378 mg, 1.50 mmol) in benzene in an identical manner to example 3 gave the title compound (390 mg, 76%).

¹H NMR (CDCl₃, 300 MHz); δ 1.10-1.25 (6H, m), 2.30-2.42 (3H, m), 2.92 (2H, d), 3.27-3.40 (1H, m), 3.50-3.65 (1H, m), 3.94 (1H, tm), 4.13 (2H, qm), 4.57-4.64 (2H, m), 6.23-6.38 (1H, m), 6.79 (2H, dm), 7.03-7.67 (15H, dm).

LCMS (electrospray): 543 (M+Na), 538 (M+NH₄), 283 (100%).

Example 60

(E, Z)-(2S)-3-[4-(3-Biphenyl-4-yl-3-p-tolyl-allyloxy)-phenyl]-2-ethoxy-propionic acid

(E, Z)-(2S)-3-[4-(3-Biphenyl-4-yl-3-p-tolyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester (example 59) (370 mg, 0.71 mmol) was hydrolyzed in an identical manner to example 2 to give the title compound (310 mg, 89%).

LCMS (electrospray): 515 (M+Na), 283 (100%).

(E, Z)-(2R)- 3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester

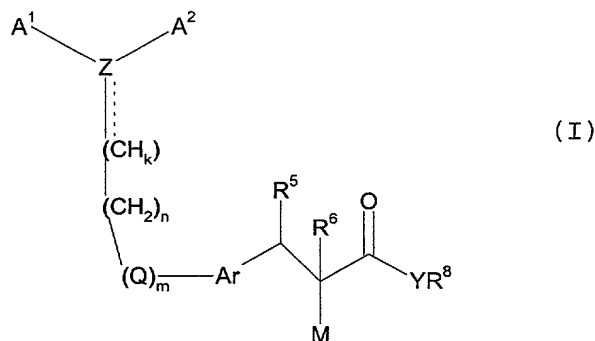
Potassium carbonate (0.25 g, 1.81 mmol) was added to a stirred solution of 4-(3-bromo-1-phenyl-prop-1-enyl)-biphenyl (0.35 g, 1.00 mmol) and (2*R*)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (0.215 g, 0.90 mmol) in dry acetone (20 ml), and the mixture heated to 60°C under reflux for 18 h. The resulting suspension was cooled to room temperature, filtered to remove inorganic products, and the solvents evaporated. The product was purified by flash column chromatography on silica gel, eluting with 15% ethyl acetate in light petroleum, to give the title compound as a colorless gum (0.40 g, 87%).

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What is claimed is:

1. A compound of formula (I)



5

- wherein A¹ and A² are independently of each other a 5-6 membered cyclic ring or a 9-10 membered bicyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro, cyano, formyl, or C₁₋₁₂-alkyl, (C₃₋₆-cycloalkyl)C₁₋₆-alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, C₁₋₁₂-alkoxy, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, acyl, acyloxy, hydroxyC₁₋₁₂-alkyl, amino, acylamino, C₁₋₁₂-alkyl-amino, C₁₋₆-dialkylamino, arylamino, arylalkylamino, aminoC₁₋₁₂-alkyl, C₁₋₁₂-alkoxycarbonyl, alkylaminocarbonyl, aryloxycarbonyl, arylalkoxycarbonyl, C₁₋₁₂-alkoxyC₁₋₁₂-alkyl, aryloxyC₁₋₁₂-alkyl, arylalkoxyC₁₋₁₂-alkyl, arylthio, C₁₋₁₂-alkylthio, thioC₁₋₁₂-alkyl, C₁₋₁₂-alkoxycarbonylamino, aryloxycarbonylamino, arylalkoxycarbonylamino, -COR¹, or -SO₂R², wherein R¹ and R² independently of each other are selected from hydroxy, halogen, perhalomethyl, C₁₋₆-alkoxy or amino optionally substituted with one or more C₁₋₆-alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

- Z is C or CR³, wherein R³ is hydrogen, halogen, perhalomethyl, C₁₋₁₂-alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, C₁₋₁₂-alkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, acyl, acyloxy, hydroxyC₁₋₁₂-alkyl, C₁₋₁₂-alkoxyC₁₋₁₂-alkyl, aryloxyC₁₋₁₂-alkyl, arylalkoxyC₁₋₁₂-alkyl, thioC₁₋₁₂-alkyl, -COR⁴, or -SO₂R¹¹, wherein R⁴ and R¹¹ independently of each other are selected from hydroxy, halogen, perhalomethyl, C₁₋₆-alkoxy or amino optionally substituted with one or more C₁₋₆-alkyl, perhalomethyl or

aryl optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

- Q is O, S or NR^{12} , wherein R^{12} is hydrogen, perhalomethyl, C_{1-12} -alkyl, C_{4-12} -alkenynyl, C_{2-12} -alkenyl, C_{2-12} -alkynyl, aryl, arylalkyl, heterocyclyl, heteroaryl, heteroarylalkyl, acyl, hydroxy C_{1-12} -alkyl, amino C_{1-12} -alkyl, C_{1-12} -alkoxycarbonyl, aryloxycarbonyl, arylalkoxycarbonyl, C_{1-12} -alkoxy C_{1-12} -alkyl, aryloxy C_{1-12} -alkyl, arylalkoxy C_{1-12} -alkyl, thio C_{1-12} -alkyl, $-\text{COR}^{13}$, or $-\text{SO}_2\text{R}^{14}$, wherein R^{13} and R^{14} independently of each other are selected from hydroxy, perhalomethyl, C_{1-6} -alkoxy or amino optionally substituted with one or more C_{1-6} -alkyl, perhalomethyl or aryl optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

- represents a single bond or a double bond;

- Ar is arylene, heteroarylene, or a divalent heterocyclic group each of which is optionally substituted with one or more halogen, C_{1-6} -alkyl, amino, hydroxy, C_{1-6} -alkoxy or aryl;

- R^5 is hydrogen, hydroxy, halogen, C_{1-12} -alkoxy, C_{1-12} -alkyl, C_{4-12} -alkenynyl, C_{2-12} -alkenyl, C_{2-12} -alkynyl or arylalkyl optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano or R^5 forms a bond together with R^6 ;

- R^6 is hydrogen, hydroxy, halogen, C_{1-12} -alkoxy, C_{1-12} -alkyl, C_{4-12} -alkenynyl, C_{2-12} -alkenyl, C_{2-12} -alkynyl, acyl or arylalkyl optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano or R^6 forms a bond together with R^5 ;

- M is OR^7 , where R^7 is hydrogen, C_{1-12} -alkyl, C_{4-12} -alkenynyl, C_{2-12} -alkenyl, C_{2-12} -alkynyl, aryl, arylalkyl, C_{1-12} -alkoxy C_{1-12} -alkyl, C_{1-12} -alkoxycarbonyl, aryloxycarbonyl, C_{1-12} -alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl or heteroarylalkyl groups optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano or M is COYR^8 ;

R⁸ is hydrogen, C₁₋₁₂alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, aryl, arylalkyl, heterocycl, heteroaryl or heteroarylalkyl groups optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

- 5 Y is oxygen, sulphur or NR¹⁰, where R¹⁰ is hydrogen, C₁₋₁₂-alkyl, aryl, hydroxyC₁₋₁₂-alkyl or arylalkyl groups or when Y is NR¹⁰, R⁸ and R¹⁰ may form a 5 or 6 membered nitrogen containing ring, optionally substituted with one or more C₁₋₆-alkyl;

10 k is an integer ranging from 1 to 2, n is an integer ranging from 0 to 3 and m is an integer ranging from 0 to 1;

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, or any tautomeric forms.

- 15 2. A compound of claim 1, wherein A¹ and A² are independently of each other a 5-6 membered cyclic ring or a 9-10 membered bicyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, C₁₋₆-alkyl, (C₃₋₆-cycloalkyl)C₁₋₆-alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₁₋₆-alkoxy, aryl, aryloxy, arylalkyl, arylalkoxy, heterocycl, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, acyl, hydroxyC₁₋₆-alkyl, C₁₋₆-alkyl-amino, C₁₋₆-dialkylamino, arylamino, arylalkylamino, aminoC₁₋₆-alkyl, C₁₋₆-alkoxycarbonyl, alkylaminocarbonyl, aryloxycarbonyl, arylalkoxycarbonyl, C₁₋₆-alkoxyC₁₋₆-alkyl, aryloxyC₁₋₆-alkyl, or arylalkoxyC₁₋₆-alkyl.

- 25 3. A compound of claim 1, wherein A¹ and A² are independently of each other a 5-6 membered cyclic ring or a 9-10 membered bicyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, C₁₋₆-alkyl, (C₃₋₆-cycloalkyl)C₁₋₆-alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₁₋₆-alkoxy, aryl, aryloxy, arylalkyl, arylalkoxy, heterocycl, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, acyl, hydroxyC₁₋₆-alkyl, C₁₋₆-alkyl-amino, C₁₋₆-dialkylamino, arylamino, arylalkylamino, aminoC₁₋₆-alkyl, C₁₋₆-alkoxyC₁₋₆-alkyl, aryloxyC₁₋₆-alkyl, or arylalkoxyC₁₋₆-alkyl.

4. A compound of claim 1, wherein A¹ and A² are independently of each other a 5-6 membered cyclic ring or a 9-10 membered bicyclic ring, optionally substituted with one or more halogen, C₁₋₆-alkyl, C₁₋₆-alkoxy or aryl.

5. A compound of claim 1, wherein A¹ and A² are independently of each other a 5-6 membered cyclic ring optionally substituted with one or more halogen, C₁₋₆-alkyl, C₁₋₆-alkoxy, or aryl.
- 5
6. A compound of claim 1, wherein Z is a carbon atom at the end of a double bond, or Z is CR³, wherein R³ is hydrogen, halogen, perhalomethyl, C₁₋₁₂-alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, C₁₋₁₂-alkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, acyl, acyloxy, hydroxyC₁₋₁₂-alkyl, C₁₋₁₂-alkoxyC₁₋₁₂-alkyl, aryloxyC₁₋₁₂-alkyl, arylalkoxyC₁₋₁₂-alkyl, thioC₁₋₁₂-alkyl, -COR⁴, or -SO₂R¹¹, wherein R⁴ and R¹¹ independently of each other are selected from hydroxy, halogen, perhalomethyl, C₁₋₆-alkoxy or amino optionally substituted with one or more C₁₋₆-alkyl, perhalomethyl or aryl optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano.
- 10
7. A compound of claim 1, wherein Z is a carbon atom at the end of a double bond, or Z is CR³, wherein R³ is hydrogen, halogen, perhalomethyl, C₁₋₆-alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₁₋₆-alkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, acyl, acyloxy, hydroxyC₁₋₆-alkyl, C₁₋₆-alkoxyC₁₋₆-alkyl, aryloxyC₁₋₆-alkyl, arylalkoxyC₁₋₆-alkyl, thioC₁₋₆-alkyl, -COR⁴, or -SO₂R¹¹, wherein R⁴ and R¹¹ independently of each other are selected from hydroxy, halogen, perhalomethyl, C₁₋₆-alkoxy or amino optionally substituted with one or more C₁₋₆-alkyl, perhalomethyl or aryl optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano.
- 15
8. A compound of claim 1, wherein Z is a carbon atom at the end of a double bond, or Z is CR³, wherein R³ is hydrogen, halogen, perhalomethyl, C₁₋₆-alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₁₋₆-alkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, C₁₋₆-alkoxyC₁₋₆-alkyl, aryloxyC₁₋₆-alkyl, or arylalkoxyC₁₋₆-alkyl.
- 20
9. A compound of claim 1, wherein Z is a carbon atom at the end of a double bond, or Z is CR³, wherein R³ is hydrogen.
- 25
10. A compound of claim 1, wherein Q is O, S, or NR¹², wherein R¹² is hydrogen, perhalomethyl, C₁₋₆-alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, aryl, arylalkyl, heterocyclyl, heteroaryl, heteroarylalkyl, acyl, hydroxyC₁₋₆-alkyl, aminoC₁₋₆-alkyl, C₁₋₆-
- 30

alkoxycarbonyl, aryloxycarbonyl, arylalkoxycarbonyl, C₁₋₆-alkoxyC₁₋₆-alkyl, aryloxyC₁₋₆-alkyl, arylalkoxyC₁₋₆-alkyl, thioC₁₋₆-alkyl, -COR¹³, or -SO₂R¹⁴, wherein R¹³ and R¹⁴ independently of each other are selected from hydroxy, perhalomethyl, C₁₋₆-alkoxy or amino optionally substituted with one or more C₁₋₆-alkyl, perhalomethyl or aryl

5 optionally substituted with one or more halogen, or perhalomethyl.

11. A compound of claim 1, wherein Q is O, S, or NR¹², wherein R¹² is hydrogen, perhalomethyl, C₁₋₆-alkyl, aryl, arylalkyl, heteroarylalkyl, or acyl.

10 12. A compound of claim 1, wherein Q is O or S.

13. A compound of claim 1, wherein Q is O.

15 14. A compound of claim 1, wherein Ar is arylene, heteroarylene, or a divalent heterocyclic group each of which can optionally be substituted with one or more halogen, C₁₋₆-alkyl or C₁₋₆-alkoxy.

15. A compound of claim 1, wherein Ar is arylene, or heteroarylene.

20 16. A compound of claim 1, wherein Ar is arylene.

17. A compound of claim 1, wherein R⁵ is hydrogen, hydroxy, halogen, C₁₋₆-alkoxy, C₁₋₆-alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl or arylalkyl optionally substituted with one or more halogen, or perhalomethyl or R⁵ forms a bond together with R⁶.

25

18. A compound of claim 1, wherein R⁵ is hydrogen, halogen, C₁₋₆-alkoxy, C₁₋₆-alkyl, or perhalomethyl or R⁵ forms a bond together with R⁶.

30 19. A compound of claim 1, wherein R⁵ is hydrogen, halogen or R⁵ forms a bond together with R⁶.

20. A compound of claim 1, wherein R⁵ is hydrogen.

21. A compound of claim 1, wherein R⁶ is hydrogen, C₁₋₆-alkoxy, C₁₋₆-alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, acyl or arylalkyl optionally substituted with one or more halogen or perhalomethyl or R⁶ forms a bond together with R⁵.
- 5 22. A compound of claim 1, wherein R⁶ is hydrogen, halogen, C₁₋₆-alkoxy, or R⁶ forms a bond together with R⁵.
23. A compound of claim 1, wherein R⁶ is hydrogen, C₁₋₆-alkoxy, or R⁶ forms a bond together with R⁵.
- 10 24. A compound of claim 1, wherein R⁶ is hydrogen.
25. A compound of claim 1, wherein M is OR⁷, where R⁷ is hydrogen, C₁₋₆-alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, aryl, arylalkyl, C₁₋₆-alkoxyC₁₋₆-alkyl, C₁₋₆-alkoxycarbonyl, 15 aryloxycarbonyl, C₁₋₆-alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl or heteroarylalkyl groups optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano.
- 20 26. A compound of claim 1, wherein M is OR⁷, where R⁷ is hydrogen, C₁₋₆-alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, aryl, arylalkyl, C₁₋₆-alkoxyC₁₋₆-alkyl, heterocyclyl, heteroaryl or heteroarylalkyl groups optionally substituted with one or more halogen or perhalomethyl.
- 25 27. A compound of claim 1, wherein M is OR⁷, where R⁷ is C₁₋₆-alkyl or M is COYR⁸ where R⁸ is defined as in claim 1.
28. A compound of claim 1, wherein M is OR⁷, where R⁷ is ethyl or M is COYR⁸ where R⁸ is defined as in claim 1.
- 30 29. A compound of claim 1, wherein R⁸ is hydrogen, C₁₋₆-alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, aryl, arylalkyl, heterocyclyl, heteroaryl or heteroarylalkyl groups optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano.

30. A compound of claim 1, wherein R⁸ is hydrogen, C₁₋₆alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, aryl, arylalkyl, heterocyclyl, heteroaryl or heteroarylalkyl groups optionally substituted with one or more halogen, or perhalomethyl.
31. A compound of claim 1, wherein R⁸ is hydrogen or C₁₋₆alkyl.
32. A compound of claim 1, wherein R⁸ is hydrogen or ethyl.
33. A compound of claim 1, wherein Y is oxygen, sulphur or NR¹⁰, where R¹⁰ is hydrogen, C₁₋₆-alkyl, aryl, hydroxyC₁₋₆-alkyl or arylalkyl groups or when Y is NR¹⁰, R⁸ and R¹⁰ may form a 5 or 6 membered nitrogen containing ring, optionally substituted with one or more C₁₋₆-alkyl.
34. A compound of claim 1, wherein Y is oxygen, or NR¹⁰, where R¹⁰ is hydrogen, C₁₋₆-alkyl, aryl, or arylalkyl groups, or when Y is NR¹⁰, R⁸ and R¹⁰ may form a 5 or 6 membered nitrogen containing ring, optionally substituted with one or more C₁₋₆-alkyl.
35. A compound of claim 1, wherein Y is oxygen.
36. A compound of claim 1, wherein k is an integer ranging from 1 to 2.
37. A compound of claim 1, wherein n and m are 1.
38. A compound of claim 1, which is
- 2-Ethoxy-3-{4-[3-phenyl-3-(4-methylphenyl)-allyloxy]-phenyl}-propionic acid ethyl ester,
2-Ethoxy-3-{4-[3-phenyl-3-(4-methylphenyl)-allyloxy]-phenyl}-propionic acid,
3-{4-[3-(2-Chloro-phenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,
3-{4-[3-(2-Chloro-phenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid,
3-{4-[3,3-Bis-(4-methoxy-phenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,
3-{4-[3,3-Bis-(4-methoxy-phenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid,
3-{4-[3-Phenyl-3-(biphenyl-4-yl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,
3-{4-[3-Phenyl-3-(biphenyl-4-yl)-allyloxy]-phenyl}-2-ethoxy-propionic acid,
2-Ethoxy-3-{4-[3-phenyl-3-(thiophen-2-yl)-allyloxy]-phenyl}-propionic acid ethyl ester,
2-Ethoxy-3-{4-[3-phenyl-3-(thiophen-2-yl)-allyloxy]-phenyl}-propionic acid,

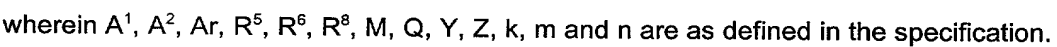
- 2-Ethoxy-3-{4-[3-phenyl-3-(pyridin-2-yl)-allyloxy]-phenyl}-propionic acid ethyl ester,
2-Ethoxy-3-{4-[3-phenyl-3-(pyridin-2-yl)-allyloxy]-phenyl}-propionic acid,
3-[4-(3, 3-Diphenyl-propoxy)-phenyl]-2-ethoxy-propionic acid ethyl ester,
3-[4-(3,3-Diphenyl-propoxy)-phenyl]-2-ethoxy-propionic acid,
5 2-Ethoxy-3-{4-[3-phenyl-3-(4-methylphenyl)-propoxy]-phenyl}-propionic acid ethyl ester,
2-Ethoxy-3-{4-[3-phenyl-3-(4-methylphenyl)-propoxy]-phenyl}-propionic acid,
3-{4-[3-Phenyl-3-(biphenyl-4-yl)-propoxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,
3-{4-[3-Phenyl-3-(biphenyl-4-yl)-propoxy]-phenyl}-2-ethoxy-propionic acid,
2-{4-[3,3-Bis-(4-methoxy-phenyl)-allyloxy]-benzyl}-malonic acid dimethyl ester,
10 (E)-(2S)-2-Ethoxy-3-{4-[3-(4-furan-2-yl-phenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid ethyl ester,
(E)-(2S)-2-Ethoxy-3-{4-[3-(4-furan-2-yl-phenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid,
(E)-(2S)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester,
(E)-(2S)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid,
15 (E, Z)-(2S)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester,
(E, Z)-(2S)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid,
3-{4-[3,3-Bis-(3-methyl-thiophen-2-yl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,
3-{4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,
20 3-{4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid,
2-Ethoxy-3-[4-(3-phenyl-3-pyridin-4-yl-allyloxy)-phenyl]-propionic acid ethyl ester,
2-Ethoxy-3-[4-(3-phenyl-3-pyridin-4-yl-allyloxy)-phenyl]-propionic acid,
(E, Z)-(2S)-2-Ethoxy-3-{4-[3-(4-methoxyphenyl)-3-thiophen-2-yl-allyloxy]-phenyl}-propionic acid ethyl ester,
25 (E, Z)-(2S)-2-Ethoxy-3-{4-[3-(4-methoxyphenyl)-3-thiophen-2-yl-allyloxy]-phenyl}-propionic acid,
(E, Z)-(2S)-2-Ethoxy-3-[4-(3-phenyl-3-p-tolyl-allyloxy)-phenyl]-propionic acid ethyl ester,
(E, Z)-(2S)-2-Ethoxy-3-[4-(3-phenyl-3-p-tolyl-allyloxy)-phenyl]-propionic acid,
(2S)-3-[4-(3,3-Diphenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester,
30 (2S)-3-[4-(3,3-Diphenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid,
(Z)-(2S)-2-Ethoxy-3-{4-[3-(4-fluorophenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid ethyl ester,
(Z)-(2S)-2-Ethoxy-3-{4-[3-(4-fluorophenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid.

- (*E*)-(2*S*)-2-Ethoxy-3-{4-[3-(4-fluorophenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid ethyl ester,
- (*E*)-(2*S*)-2-Ethoxy-3-{4-[3-(4-fluorophenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid,
- (2*S*)-3-{4-[3,3-Bis-(4-methoxyphenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,
- 5 (2*S*)-3-{4-[3,3-Bis-(4-methoxyphenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid,
- (2*S*)-3-[4-(3,3-Di-*p*-tolyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester,
- (2*S*)-3-[4-(3,3-Di-*p*-tolyl-allyloxy)-phenyl]-2-ethoxy-propionic acid,
- (*Z*)-(2*S*)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid,
- (*Z*)-(2*S*)-3-{4-[3-(4-Bromophenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl
- 10 ester,
- (*Z*)-(2*S*)-3-{4-[3-(4-Bromophenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid,
- (2*S*)-3-[4-(3,3-Bis-biphenyl-4-yl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester,
- (2*S*)-3-[4-(3,3-Bis-biphenyl-4-yl-allyloxy)-phenyl]-2-ethoxy-propionic acid,
- (2*S*)-3-{4-[3,3-Bis-(4-bromophenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,
- 15 (2*S*)-3-{4-[3,3-Bis-(4-bromophenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid,
- (*Z*)-(2*S*)-2-Ethoxy-3-{4-[3-(4-furan-2-yl-phenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid ethyl ester,
- (*Z*)-(2*S*)-2-Ethoxy-3-{4-[3-(4-furan-2-yl-phenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid,
- (*E*)-(2*S*)-3-{4-[3-(4-Bromophenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl
- 20 ester,
- (*E*)-(2*S*)-3-{4-[3-(4-Bromophenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid,
- (2*S*)-3-{4-[3,3-Bis-(4-furan-2-yl-phenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,
- (2*S*)-3-{4-[3,3-Bis-(4-furan-2-yl-phenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid,
- (*E*, *Z*)-(2*S*)-3-[4-(3-Biphenyl-4-yl-3-*p*-tolyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl es-
- 25 ter,
- (*E*, *Z*)-(2*S*)-3-[4-(3-Biphenyl-4-yl-3-*p*-tolyl-allyloxy)-phenyl]-2-ethoxy-propionic acid, or
- (*E*, *Z*)-(2*R*)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester;
- 30 or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, or any tautomeric forms.

39. A pharmaceutical composition comprising, as an active ingredient, an effective amount of a compound of claim 1, together with a pharmaceutically acceptable carrier or diluent.

40. The pharmaceutical composition of claim 39 in unit dosage form, comprising from about 0.05 to about 100 mg of the compound.
- 5 41. The pharmaceutical composition of claim 40 in unit dosage form, comprising from about 0.1 to about 50 mg of the compound.
42. The pharmaceutical composition of claim 39 which is administered by the oral, nasal, transdermal, pulmonary, or parenteral route.
- 10 43. A method for treating or preventing conditions mediated by nuclear receptors, the method comprising administering to a subject in need thereof an effective amount of a compound of claim 1.
- 15 44. The method of claim 43, wherein the nuclear receptors are the Peroxisome Proliferator-Activated Receptors (PPAR).
45. A method for treating or preventing diabetes and/or obesity, the method comprising administering to a subject in need thereof an effective amount of a compound of claim 1.
- 20 46. The method of claim 43, wherein the effective amount of the compound is in the range of from about 0.05 to about 100 mg per day.
47. The method of claim 46, wherein the effective amount of the compound is from about 0.1 to about 50 mg per day.
- 25

Disclosed are novel compounds of formula (I)



- 10 These compounds are useful in the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR). Such conditions include diabetes and obesity.

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY
(Includes Reference to PCT International Applications)

Attorney's Docket Number:
5697.200-US

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

New Compounds, Their Preparation and Use

The specification of which (check only one item below):

☐ is attached hereto

☒ was filed as United States application

Application No. To Be Assigned

on April 18, 2000

and was amended

on _____

☐ was filed as PCT international application

Number _____

on _____

and was amended under PCT Article 19

on _____

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by an amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability of this application in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim priority benefits under Title 35, United States Code, §119 of any provisional or foreign application(s) for patent or inventor's certificate or of any PCT international applications(s) for patent or inventor's certificate or of any PCT international applications(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR U.S. PROVISIONAL/FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (if PCT, indicated "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119	
DK	PA 1999 00533	20 April 1999	<input checked="" type="checkbox"/> YES	<input type="checkbox"/> NO
US	60/132,193	3 May 1999	<input checked="" type="checkbox"/> YES	<input type="checkbox"/> NO
			<input type="checkbox"/> YES	<input type="checkbox"/> NO
			<input type="checkbox"/> YES	<input type="checkbox"/> NO
			<input type="checkbox"/> YES	<input type="checkbox"/> NO

Attorney's Docket Number:
5697.200-US

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT
UNDER 35 U.S.C. 120.

POWER OF ATTORNEY										As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute <i>this application</i> and transact all business in the Patent and Trademark Office connected therewith									
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a) α -methylstyrene		b) α -methylstyrene		c) α -methylstyrene		d) α -methylstyrene		e) α -methylstyrene		f) α -methylstyrene		g) α -methylstyrene		h) α -methylstyrene		i) α -methylstyrene		j) α -methylstyrene		k) α -methylstyrene		l) α -methylstyrene		m) α -methylstyrene		n) α -methylstyrene		o) α -methylstyrene		p) α -methylstyrene		q) α -methylstyrene		r) α -methylstyrene		s) α -methylstyrene		t) α -methylstyrene		u) α -methylstyrene		v) α -methylstyrene		w) α -methylstyrene		x) α -methylstyrene		y) α -methylstyrene		z) α -methylstyrene																																																	
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon

Signature of Inventor 1	Signature of Inventor 2	Signature of Inventor 3
Date	Date	Date
Signature of Inventor 4	Signature of Inventor 5	Signature of Inventor 6
Date	Date	Date
Signature of Inventor 7	Signature of Inventor 8	Signature of Inventor 9
Date	Date	Date